Joint Action on HTA 2012-2015

Methodological Standards and Procedures (MSP) for Full core HTA content development

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Was developed by Work Package 4 -

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List of abbreviations

- COI – Conflict of Interest
- CUR – Current use of the technology (Domain)
- DOICU – Declaration of Interest and Confidentiality Undertaking
- ECO – Costs, economic evaluation of the technology (Domain)
- EFF – Effectiveness of the technology (Domain)
- ET – Editorial Team
- ETH –Ethical aspects of the technology (Domain)
- EUnetHTA – European Network for Health Technology Assessment
- GL - Guideline
- HTA – Health Technology Assessment
- I – Investigator
- JA1 – Joint Action 1
- JA2 – Joint Action 2
- LEG – Legal aspects of the technology (Domain)
- LP – Lead Partner
- MSP – Methodological Standards and Procedures
- ORG – Organisational aspects of the technology (Domain)
- PI – Primary Investigator
- POP Database – Planned and On-going Project database
- SAF – Safety of the technology (Domain)
- SAG – Stakeholder Advisory Group
- SOC - Social aspects of the technology (Domain)
- SOP – Standard Operating Procedure
- STK – Stakeholder
- TEC – Description and technical characteristics of technology (Domain)
- WP – Work Package

Why produce guidance ?

Aim

The aim of this document is to guide the production of full Core HTA information based on collaboration of different European organizations using the EUnetHTA available tools. Where guidance on specific issues is already available, the source is cited and in some cases extract of contents is reported.

Evidence base

The 3-Year work plan of Work Package 4 of EUnetHTA JA2.

Practical guidance

The most powerful rationale for the EUnetHTA network is sharing and collaboration to enhance efficiency and relevance of information for all users. As a consequence a common set of procedures and standards, based on experience applied to scientific knowledge, will aid and speed up homogeneous production.

This guidance, first produced at the same time as the first JA2 Core HTA, aims at providing practical help when it is most needed. The document is updated accordingly with ongoing experience and changes in collaborations process and models, as well as with possible scientific and methodological developments both in WP4 and in other WPs of EUnetHTA JA2 .

The document provides guidance which can be improved within the collaboration.

Composition and Terms of Reference of writing team

To write the first draft of this document an extended writing team was organized through a call for volunteers. This resulted in the Writing Teams line-up.

Chapter	Writing Team
Why produce guidance now [rationale for producing guidance on how to do things] **The story so far**. [Background to the project with history, aims and evolution] **JA2 WP4 aims and production outputs** [summary of why and what WP4 will produce] **Description of the content and use of the JA1 feed-back.** [how the JA1 feed back was incorporated in the guidance]	Tom Jefferson (Agenas) Marina Cerbo (Agenas) Kristian Lampe (THL) Francesca Gillespie (Agenas)
Stakeholder (STK) involvement process and dealing with Conflict of interest and confidentiality of data in pilots [methods to involve stakeholders and carry out validation]	Mirjana Huic (AAZ) Francesca Gillespie (Agenas)
Project management and forming teams [how to form teams] **Order of domain work** [how to approach domain work and how to communicate across domains and with coordination]	Kristian Lampe (THL) Marina Cerbo (Agenas) Nicola Vicari (Agenas)
National production [how to promote the use of core HTA information]	Marina Cerbo (Agenas) Marco Marchetti (A. Gemelli-UCSC) WP4 Sub group 3
Carrying out evidence searches [how to construct, run, store and update searches]	Tom Jefferson (Agenas) Francesca Gillespie (Agenas)
Domain specific issues: Current use of the technology(CUR) [methods to develop domain content]	Luciana Ballini (ASSR – RER)
Domain specific issues: Description and technical characteristics of technology (TEC) [methods to develop domain content]	Antonio Migliore (Agenas) Daniela Pertl (GOG)
Domain specific issues: Safety of the technology (SAF) [methods to develop domain content]	Luciana Ballini (ASSR – RER)
Domain specific issues: Effectiveness of the technology	Luciana Ballini (ASSR – RER)

(EFF) [methods to develop domain content]	Luca Vignatelli Leonor Varela (Avalia-t) Susanna Maltoni (ASSR-RER)
Domain specific issues: Costs, economic evaluation of the technology (ECO) [methods to develop domain content]	Elpida Pavi (NSPH) Eleftheria Karampli (NSPH)
Domain specific issues: Ethical aspects of the technology (ETH) [methods to develop domain content]	Dario Sacchini (A. Gemelli-UCSC) Pietro Refolo (A. Gemelli-UCSC) Roberta Minacori (A. Gemelli-UCSC) Marta Lopez de Argumedo (Osteba)
Domain specific issues: Organisational aspects of the technology (ORG) [methods to develop domain content]	Marco Marchetti (A. Gemelli-UCSC) Americo Cicchetti (A. Gemelli-UCSC) Giorgia Tedesco (A. Gemelli-UCSC) Angelica Carletto (A. Gemelli-UCSC) Daniela D'Angela (CEIS) Federico Spandonaro (CEIS) Barbara Polistena (CEIS)
Domain specific issues: Social aspects of the technology (SOC) [methods to develop domain content]	Alessandra Lo Scalzo (Agenas)
Domain specific issues: Legal aspects of the technology (LEG) [methods to develop domain content]	Marina Casini (A. Gemelli-UCSC) Emanuela Midolo (A. Gemelli-UCSC)
General review	Marina Cerbo (Agenas) Nicola Vicari (Agenas)

Structure of the guidance

The content of the guidance is primarily practical, relying on the experience gained during JA1 and JA2. For each domain or topic, brief initial guidance will allow researchers to follow at least a common thread. The aim of each chapter is NOT to provide an exhaustive treatise of description of the methods used in each domain or topic. Such sources represent the basis for the MSP but their inclusion in the MSP would introduce repetition and increase the size of the document.

The suggestions in this document are amenable to editing and change as increasing experience is gained. As such, the suggestions are not meant to be definitive and should be read in conjunction with the content of Appendix 1 of the 3-year work plan.

The purpose of this document is to facilitate the collaboration among researchers operating in different contexts and with different backgrounds. This cannot be achieved if communication is difficult or if information is scattered in different documents.

The content is divided in two Parts : **Part 1** addresses the general issues in joint assessments, **Part 2** addresses scientific issues relevant to domain work.

Each chapter consists of:

-Title

- *Aim* :a brief statement of the aim of the chapter

- *Evidence base* : a summary of the evidence base or applied methods at the basis of the guidance. If none exist, this is clearly stated.

- *Practical guidance* : “how to” description in which the authors explain the practical steps of the realization of the task. This is the part in which past-experience provides practical help to complete the task.

- *Bibliography:* a list of relevant sources used

The text has not been proof read or copy edited.

PART 1

1.1 The story so far.

The first project to establish a sustainable European Network on Health Technology Assessment (HTA) was set up in 2005 with funds from the European Commission and the Council of Ministers. The first project included a group of 35 organizations in 27 European countries with the coordination of the Danish Centre for Evaluation and HTA.

The main strategic objective of the network was to actively connect different HTA agencies and institutions, at national and/or regional level to enable an effective exchange of information and to support policy makers' decisions.

The first step was to set-up an organizational framework for a European Network on HTA and the development of practical enabling tools and services. After the successful completion of the EUnetHTA Project (2006-2008) the EUnetHTA Collaboration further developed the basis for a sustainable and permanent collaboration for HTA in Europe. In 2009 25 Founding Partners of EUnetHTA Collaboration joined forces with other partners and the European Commission to implement results of the previous projects through the first Joint Action (JA1) on HTA 2010-2012: a total of 55 organizations committed their resources to participate in the planned activities within the framework of the EUnetHTA JA1.

The overarching objective of the EUnetHTA JA1 was to put into practice an effective and sustainable HTA collaboration in Europe bringing added value at the European, national and regional level.

The second Joint Action (JA2) started in October 2012. JA2 could lead to the creation of a permanent and sustainable European Network for HTA through the development of a general strategy, principles and an implementation proposal, according to the requirements of Article 15 of the Directive for cross-border healthcare (2011/24/EU).

Within the JA2, Work Package 4 has the remit to:

- Test the capacity of national HTA bodies to produce structured core HTA information (full core/rapid HTAs) together and apply it in national context (including collection of data on costs and overall efficiency of the production in the network).
- Implement, pilot and further develop models and tools as well as production processes to support collaborative production of core HTA information with reinforced secretariat and coordination function.

1.2 JA2 WP4 aims and production outputs

Aim

"The aim of JA2 WP4 is to produce 3 core HTAs (they can be both pharmaceutical and non-pharmaceutical interventions) and up to 20 linked national HTA reports, while further developing production methods in readiness for the creation of the permanent network.

Evidence base

EUnetHTA WP4 3-year Workplan.

Practical guidance

Producing core HTAs is a complex business, as it reflects the reality use of the intervention being assessed.

Such an undertaking has three main characteristics.

First, it must be a multidisciplinary effort reflecting the complex reality of the interventions and its uses.

Second, production must tread the tightrope of producing coherent and authoritative structured HTA information which is at the same time general, exhaustive, and usable as a basis for local use at national or subnational level.

Third, network production means avoidance of redundancy and duplication as all members of the network are free to propose and join and contribute to projects on topics of importance to their body or institution. Sharing of resources enhances efficiency and relevance.

1.3 Description of the content and use of the JA1 feed-back.

Aim

To explain how the JA 1 feedback was incorporated in the guidance. JA1 feedback is an important part of the baggage of experience in using the HTA Core Model.

Evidence base

The methodology applied was gathering relevant validation results of JA1 and delivering information on the use of the HTA Core Model and HTA Core Model On-line Tool to relevant working groups.

Practical guidance

We describe the process of making relevant JA1 validation information available to working groups.

The Validation of JA1 consisted of the following four Surveys:

- Core HTA Production Survey submitted to persons who participated in core HTA production
- Screening Model Survey submitted to member agencies of EUnetHTA and INAHTA
- Online Tool and Service Survey submitted to EUnetHTA Agencies + WP4 SAG
- Core HTA Content and Format Survey submitted to member agencies of EUnetHTA and INAHTA + WP4 SAG + Public Consultation

After a first analysis of results an official description of the validation process was made available in the Technical Report of Joint Action 1.

At the first e-meeting of JA2 the following critical issues about the validation results were presented along with considerations of how we can improve them:

- Roles and work load specifications (Reviewers, Primary Investigators, Investigators, Editorial team, Project Leader, Coordinator, etc.)
- Topic selection, Prioritization, Stakeholder involvement
- Collaborative model: mix?
- Lack of methodological guidance
- Conflicts of interest handling
- Problems with model applications
- Overlapping issues within and across domains
- Domain work cascade
- Standardization of evidence handling

Subsequently validation results where further analyzed by broad topics and textual comments were examined to identify similar and otherwise most relevant feedback.

Target working groups for receiving relevant information where identified and results were made available accordingly.

The first identified groups were the MSP working group and expert groups working on the update of the HTA Core Model within WP8. The following is a non-exhaustive list of the major topics of the grouped validation results received:

- Overall feasibility of the core HTA concept
- Key features of the HTA Core Model
- Core HTA content and format
- Experience in using the Screening Model, the Online Tool and Service, as well as the Collaborative Models and Final products.
- The experience acquired within the process
- Screening Core HTA model

Bibliography

At the end of JA1 users and researchers involved in the use of the CM were asked for their opinions and the resuts of this in-house survey form the basis for the comments.

1.4 Topic Notification and Selection procedure (WP4 only)

The first step in the production of any core HTA is a procedure for topic notification and selection.

The procedure adopted in JA2 is based on the experience of the JA1 and is divided into two parts:

1. Notification - identifying to the whole group interventions of interest (“technologies”).

Each EUnetHTA member and WP4 Stakeholder Advisory Group (SAG) plus DG Sanco can notify and nominate as many technologies as they want using the form in **Appendix 1**. Notification is carried out on individual forms (i.e. one notification, one form). The form must be completed using the most up-to-date information available.

Completed forms are returned electronically to the project manager by a set date. Once the completed forms are received, the project manager carries out a face assessment to identify vague notifications (see the examples at page 1 of the form) and notifications which appear to contain

mistakes. These are returned to the originators for clarification. Incomplete forms are excluded and are not further processed.

The following rules apply:

- Multiple notifications of the same technology are counted as one.
- Unclear of incomplete notifications will be deleted
- Once there is a consolidated list, this is circulated to WP4 members and SAG members.

2. Selection - members are asked to select the technology which will be the topic of the core HTA.

- All WP4 partners and SAG members plus DG Sanco are asked to express a preference for no more than three technologies of interest to them. See Appendix 6 for specimen call to vote.
- Preferences are expressed by giving the scores 1, 2 and 3 in increasing order of importance, 3 being the most important and 1 the least important (each score can only be given once to one technology). "Important" means important to the agency or body at the time of notification and voting. If the voting body has a national remit, importance has a national perspective.
- The resulting scored consolidated list is then shared and:
    - If there is a clear “winner” (a technology which has scored more 3s that the others), this will be selected as a working topic with the runner up(s) as reserve(s). At present No SUMRANK is done (i.e. no aggregate scoring to define rank).
    - If there is no clear winner (there is more than one technology with the same 3 scores), the score sheet with the top scoring technologies will be circulated for a quick (3 days) further round of voting until a clear winner emerges.
- All lists of notified technologies will be made available for information, to facilitate collaboration amongst notifiers and to form the basis for further selection. See **Appendix 2** for specimen notification of selected technology.
- Form originators may want to notify the same technologies they have already listed in the Planned and Ongoing Projects (POP) database.

1.5 Project management and forming teams

Aim

The aim of this chapter is to provide an overview of how the overall management of a core HTA project and expert collaboration are organised.

Evidence base

The contents of this chapter are based on practical experience and participants' feedback from seven previous core HTA projects within the EUnetHTA Project (2006-2008) and EUnetHTA Joint Action 1 (2010-2012) and JA2 (2012-2015).

Practical guidance

Production of a core HTA is an extensive and challenging effort, bringing together many researchers with different scientific and geographical backgrounds. Consequently the project requires firm coordination by

dedicated persons acting as project leaders. The coordination should not rely on one person only. Preferably the task should be divided between 1-3 persons to ensure continuity in case of changes of employers as well as of planned and unexpected absences from work (sabbaticals, vacation periods, sick leave).

Following the choice of the technology the project Coordinator performs the recruitment of researchers' team accordingly with partners' availability (and) interest in assessing the topic.

Apart from the coordinators, people within a project group are divided into teams working on different domains. Each of these *domain teams* should have at least one person as *primary investigator (PI)*. The PI (or PIs) bears the primary responsibility within one domain for the core HTA production process - from project planning to delivering the final version of the core HTA information collection. The PIs write the majority of the core HTA contents, supported by one or more *investigators (I).*

Each domain team should have one or more investigators that actively support the PI in his/her work. Investigators assist in writing and formulating the contents, and they can perform certain agreed-on tasks for the domain. The number of investigators depends on the available resources, but the project leaders should ensure that each domain has at least two persons actively participating as researchers, and that adequate expertise both on the topic and on the domain's typical research methodologies is available, as specified in the "*Policy for HTA Core Model and core HTA information"*.

In addition to active researchers, each domain team should have a group of *internal reviewers (IR)* who support the investigators' work by providing ideas, reading and commenting drafts and ensuring adequate geographical and health system views. The aforementioned policy sets as minimum requirement that the reviewers must come from another organisation in another country than the investigators. Based on experience from earlier core HTA projects, however, an adequate number of reviewers per domain to ensure adequate distribution of views from different settings should be recruited. Reviewers should be regarded as active members of the domain team, not as external peer-reviewers.

The detailed working methods and order, as well as timelines, should be agreed on by the members of each domain team in collaboration with the project leaders. The PI has the primary responsibility from the domain team's side to keep contact with the project leaders and to bring the practical work forward within agreed-on timeline.

An *editorial team* (ET) should be set up for each core HTA project to support the project leaders. The ET discusses challenges and solutions for problems within various domains. Often similar challenges are identified within more than one domains and different domains should seek shared solutions to problems. One person from each domain should be assigned to the ET. The PI is the preferred choice as representative of his/her domain, but the task can also be allocated to any other investigator.

Practical experience has shown the convenience of forming teams with on PI coordinating more than one domain (sometimes called "domain clusters") perhaps with enlarged investigator teams preparing 2 or the domain in one cluster under the same PI:

Bibliography

"Policy for HTA Core Model and core HTA information"

1.6 Stakeholder (STK) involvement process and dealing with Conflict of interest and confidentiality of data

Aim

To explain guidance on who, how and when involve Stakeholders (STK) keeping track of results; to explain procedure on how to deal with Conflict of interest and confidentiality of data.

Evidence base

Literature on appropriate Stakeholder involvement are summarized here. According to these data there is no single standard way of implementing STK involvement. Therefore our guidance will be based on literature and past JA1 experience while working through relevant gaps relative to STK involvement and Conflict of interest and confidentiality issues. EUnetHTA policy and SOP on STK involvement define the rules applied in the Network.

Definition of STK

STKs are groups or organizations which will potentially be affected by, or have an interest in and may in a consultative role influence the actions or aims of an organization, project or policy directions (Nielsen 2009).

The major categories are: Consumer (general public, patient, and caregiver); Clinician (Health Professional); Policymaker; Researcher; Research Funder; Insurer/Payer; and Manufacturer (Table 1) (O'Haire 2011).

Table 1. Definitions of Stakeholder groups (original table from O'Haire 2011)

Stakeholder	Definition
Consumer (general public, patient, and caregiver)	An individual or advocacy group representing individuals who use health care services (e.g., patients and their families) and/or who is a member of the community (e.g., patient, parent, neighbor) • General public • General public advocacy group • Individual patient with condition/disease • Individual patient without condition/disease • Patient advocacy group – condition/disease specific • Patient advocacy group – not condition/disease specific • A person acting as a proxy or providing care to a patient with condition/disease
Clinician (Health Professional)	Health care provider (academic, rural/frontier, community) • Condition/disease specific • Not condition/disease specific • Practicing/nonpracticing Medical organizations • Condition/disease specific • Not condition/disease specific
Policymaker	An individual or organization who is involved in health care policy (e.g.,local, state, provincial and Federal legislators and staff) • Medical organizations

	• Governmental organizations (e.g., VA, AHRQ, government officials)
Researcher	An individual who conducts and/or facilitates research activities: • Basic science • Translational science • Clinical science • Research methodology • Health service • Systematic review
Research Funder	A public or private organization that funds research (e.g., National Institute of Health, Department of Defense, Robert Wood Johnson Foundation, Susan G. Komen Foundation, American Cancer Society)
Insurer/Payer	An organization or agency that pays for health-related goods and services (e.g., Blue Cross Blue Shield, Medicaid, Medicare) or a business group that pays for health insurance (e.g., employers and government)
Manufacturer	A business group that produces health-related items (e.g., pharmaceuticals and medical devices)

The following four types of STK groups have been identified as particularly important for the EUnetHTA Joint Action: 1. Patient and healthcare consumer organizations; 2. Healthcare providers (professionals and hospitals); 3. Payers and 4. Industry, with clear standard operating procedures and stakeholder involvement policy described (*http://www.eunethta.eu/outputs/eunethta-ja-stakeholder-involvement-standard-operating-procedures-sop, https://www.eunethta.eu/outputs/eunethta-ja-stakeholder-involvement-policy**).***

Reasons and key components of STK *involvement*

A KCE report (Pierart J 2012) listed reasons to involve STKs: to provide legitimacy or credibility to the HTA institutions; to promote EBM practices and EBM culture; prevent disagreement or conflicts; improve acceptance of results and increase impact; enhance relevance of research and to reduce duplication.

STK involvement is seen as serving the principles of transparency, accountability, participation, objectivity, EB outcome, patient-oriented outcome, scientific work. Criteria of effective STK involvement are: to be involved at an early stage of the project; in transparency (to clarify confidentiality issues and publication rules, task to do and planning, amount of work needed (the number of meetings) and task to do); mutual learning; and satisfaction.

Key components of STK involvement written in this report are: STK identifications and analysis; communication at an early stage; STK consultation throughout the project development process; dialogue in case of controversies; management of STK comments; STK involvement in project monitoring; regular feed-back to STK and skills to manage the process of STK involvement.

Different methods of STK *involvement*

There are different methods to involve STKs in the HTA process. The actual choice will depend on the precise set of circumstances and on the expected outcome (Table 2) (Pierart J 2012).

Table 2. Different methods of STK involvement

Methods of STK involvement
On-site visits
Individual interviews with typical STK
Focus groups
Discussion fora (meeting with 8-10 STK to discuss contentious points, project scoping groups, inventory group, rating groups)
Delphi methods
Consensus conferences
Online discussion groups
Surveys (web, telephone, paper self-administered)
Workshops
Use of social media

Practical guidance

This section represent a “how to” description on the practical steps of the realization of the task, with a description of the most common pitfalls. Maximum use of past experience is made here to give practical help to complete the task.

Past experience:

- Very little useful feedback (from scoping to comments on drafts) was provided in the JA1.
-The process of STK involvement was not clear enough and there was a need to improve transparency.

Suggested process:

STKs will be involved in different ways and at different timesin WP4 activities, according to the EUnetHTA Stakeholder Involvement Policy (SOP), Methodological Standards and Procedure (MSP) and needs expressed by Domain teams. **Appendix 3** contains a supportive Template to be used by Project Leaders to track STK involvement.

The four different ways of STK involvement will be through:

1. Stakeholder advisory group (SAG)
2. Specific product assessments
3. Public consultations
4. Expert meetings

1) STK advisory group (SAG)

WP4 invites STK Forum participants to appoint representatives with specific expertise in the assessment of medical devices, procedures and diagnostics into the WP4 Stakeholder Advisory Group (SAG). Each person

participating in this group should have a clear mandate from the Forum participant. The mandate should be agreed upon between the Forum participant and the Secretariat and communicated to WP4 LP by the Secretariat. To ensure effective communication between the partners of WP4 and the SAG, the following feedback method should be used: if there is more than one representative from any given Forum participant, their feedback should be collated into one response, resulting in one response per Forum participant. The number of representatives per Forum participant is limited to three; it is however possible to change representatives between 2012 and 2015 based on the specific expertise that is needed. This policy applies to situations where major feedback is sought on preliminary WP4 documents and activities. SAG feedback was elicited for the following activities (including timing):

- WP4 Methodological Standards and Procedure Manual, draft and final text (for a period of 14 days);
- Each Topic proposal, prioritization and selection process, according the Topic Notification and Selection Procedure (for a period of 7 days);
- Each Core HTAs Project Protocol (for a period of 7 days);
- Each Core HTAs Drafts (the final pre-SAG draft) for a period of 14 days. This may be too short a period and in future 3 weeks may be considered

Comments and feedback are implemented if relevant.

Comments and feedback will be published in the Stakeholder Forum Area of the Eunethta.eu web site.

2) Specific product assessments (full Core HTAs)

Mandatory STK involvement includes:

- Contact with the respective manufacturer at the beginning of the assessment to elicit information (e.g. C/E mark, on-going studies, available evidence). Whenever possible, the EUnetHTA submission file for other technologies shall be used as developed. In addition, the draft Project Plan (Protocol) will be sent to the manufacturer for feedback (for a period of 7 days);
- An invitation to the SAG to comment on the draft Project Plans (Protocols);
- Commenting on the draft version of a full Core HTA (which will be made accessible on the EUnetHTA website);
- At least 1 clinical expert to review the second draft of the full Core HTA (for a period of 7 days).

Comments and feedback is implemented, if relevant.

If further clarification/details are required, further STKs who may be involved are:

- Contacts of respective providers/clinicians of technology (surgeons, etc.) in the scoping phase (for a period of 7 days) to have detailed information on the technology use;
- Contacts of the respective patient group (e.g. for support on patient-relevant endpoints) at the beginning of the assessment (for a period of 7 days).

Comments and feedback are implemented, if relevant.

Questionnaire *surveys* for retrieving more information on the use of a technology are planned separately for Manufacturers and EUnetHTA WP Partners and carried out by the Coordinator of WP4, Agenas, as Lead partner of WP4 EUnetHTA JA2. Questions for these Surveys should be prepared by each Domain Primary Investigator, in close cooperation with each Domain teams (for example, data on marketing authorization, CE mark, reimbursement status, national guidelines, clinical studies in progress, non-published data...), and sent to the Coordinator. The time frame for returning the answers by mail is 10 days. Upon receipt the Coordinator should send the answers to the Primary investigator of each Domain.

Templates for these Surveys are in **Appendix 4**.

3) Public consultation (including timing):

- Final version of the WP4 Methodological Standards and Procedure Manual (on the EUnetHTA website for a period of 30 days)
- Final version of each full Core HTA (on the EUnetHTA website for a period of 30 days)
- Individual Project plans (Protocols) for each pilot full Core HTA (will be available on the EUnetHTA website for a period of 10 days)

Comments and feedback should be implemented in the final deliverables (if relevant).

To increase transparency, authors of full Core HTA should reply to all STK comments using the Authors' Reply Template.

All **Templates** (WP4 EUnetHTA JA2 Stakeholders Consultation templates on the draft Core HTA Protocol, draft Core HTA Report, final Core HTA Report; WP4 EUnetHTA JA2 Authors Reply Form on Stakeholders Consultations) are in **Appendix 5**.

Comments and feedback will be published in the Stakeholder page of the Eunethta.eu website.

4) Expert meetings

Expert meetings with clinicians, experts, manufacturers, etc. can be organized by Core HTA Coordinator to discuss emerging issues from ongoing work and share the experience/lessons. Such meetings are useful at various stages of the work, but especially before finalisation of the protocol and to discuss findings. Experience has taught that efforts to engage STKs and maintain good communication throughout are seldom wasted. As well researchers these meetings may involve STKs.

Conflict of interest and confidentiality of data in pilots

Declaration of Interest and Confidentiality Undertaking (DOICU).

Conflicts of interest are handled according to EUnetHTA JA2 SOP. As conflict of interest may be topic-dependent, conflict of interest declarations will be collected from authors and reviewers involved in a specific assessment by the Lead Partner on the DOICU Form, see **Appendix 6**. Authors and reviewers who declare a conflict of interest will be excluded from parts of or the whole work under this specific topic by Lead Partner decision. However, they may still be included in other assessments.

If external experts are involved in WP4 conflict of interest declarations will be collected from them regarding the topic, by the Lead Partner using the COI Form. External experts who declare conflict of interest will be excluded from parts of, or the whole work under this specific topic, by Lead Partner decision. However, they may still be included in other assessments.

Handling of confidential data:

It is assumed that confidentiality agreements are standard practice for the WP4 organizations or institutions when hiring personnel. As a result, no separate confidentiality agreements will be drafted for participation in pilots. Individual WP4 partner organizations or institutions (not coordinating agencies or the EUnetHTA Secretariat) are responsible and accountable for the deliverance and maintenance of confidentiality agreements for participating in assessments.

Transparency of STK involvement will be increased by clear process, methods, template, and feedback description, as well as a clear process of dealing with conflict of interest statements.

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Appendices

Appendix 3 Stakeholder Involvement Template (Project Leader overview)

Appendix 4 Survey for Manufacturer; Survey for WP4 Partners

Appendix 5 Stakeholders Consultation Form; Authors Reply Form on Stakeholders comments

Appendix 6 Conflict of Interest Declaration Form

PART 2

2.1 Order of domain work

Aim

The aim of this chapter is to provide guidance on planning and executing the practical research work of the nine domain teams working on a core HTA.

Evidence base

The contents of this chapter is based on practical experience and participants' feedback from seven core HTA projects within EUnetHTA Project (2006-2008) and EUnetHTA Joint Action 1 (2010-2012) and Joint Action 2 (2013-2015) some of which are documented in respective technical reports.

Practical guidance

The guidance in this chapter presumes that the topic of the core HTA has been selected and the domain teams have been set up according to the previous chapter. Consequently, the guidance focuses on the period during which the domain teams perform the following activities:

1. design the project protocol for the HTA Core Model Online,
2. design the research protocols of different domain teams, and
3. find answers to the research questions.

The period ends in a finalized manuscript that is submitted for publication as a *collection of core HTA information* within the HTA Core Model Online. Like topic selection, the publication approval process is beyond the scope of this chapter.

There are two specific reasons for the need for good coordination between the domain teams. These deal with information relations and possible control ("choke") points.

Information relations across domains

First, the domain teams inevitably need to deal with information that is related to the work of other domains. Two main types of relations exist.

The relation can be *sequential*, meaning that the team working on domain A needs specific information from the team working on domain B before it can answer certain research questions within domain A. For example the ECO domain needs information on effectiveness from EFF domain to answer questions on cost-effectiveness.

The relation can also be about (fully or partly) similar *content* of research, i.e. research questions that have something in common. The assessment elements within various domains can sometimes be completely similar or at least their content partly overlapping. In these cases the two domain teams should collaborate when answering such questions. In these cases the domain teams should agree on witch team provides the initial answer that is then reviewed and amended by the other team(s) to cover their viewpoints and needs. In the case of partial similarity, each domain team should work on their own research question(s) and share information with the others. For example shared literature searches may make the work more efficient even if the answers are kept separate.

Control points

Some events within the core HTA production process may make the continuation of the project meaningless. Such a situation might, for example, arise if the research within the EFF domain concludes that the effectiveness of the technology being assessed is clearly inferior or nil compared to the comparator technology (i.e. there is strong "evidence of no effect"). In that case it might be more sensible to halt the whole project and direct the research resources elsewhere rather than to continue studying all the research questions yet waiting to be answered in some other domains.

While such a decision might be useful in practice, the criteria and procedures for making such decisions have not been discussed sufficiently to issue explicit advice on such choke points in core HTA projects within JA2. Some think that the issue might not be as simple as it first seems to be. The multi-disciplinary nature of the core HTA projects makes defining a simple sequence of research within various domains with all possible important choke points very difficult. Effectiveness - or lack thereof - is not the only characteristic of a technology that would define whether it is useful to continue a project or not. Safety may be a critical feature of a technology (as in the old principle of *"primum non nocere"*). Similarly important findings may be made in any domain of the HTA Core Model. While it may be possible to define explicit choke points in the future, these should be identified, analysed and discussed. Acceptance of such a viewpoint undermines the central function of HTA, that of helping decision makers choose the best possible intervention. In practice this means choosing those intervention which have the best cost-effectiveness profile relative to the others. Such a judgement is not possible initially on the basis of dimensions other than effectiveness (although all other dimensions contribute to the final assessment). In addition such reasoning would lead to a formulary full of ineffective or unproven interventions for which a harm profile is deemed satisfactory. This is a situation which is difficult to reconcile with the HTA perspective.

Order of work

Based on the information relations, the following table summarizes the recommended order of work within domains. To provide structure for the timeline the domain team work is divided into quarters. Considering that this phase typically would take anything between 6 and 12 months, the actual time allocated for each quarter would be between 1,5 to 3 months.

Preparatory work, including preparation of relevant protocols and reading other teams' drafts is marked in Light green.

An active phase of research within the domain is marked in Dark green.

Time →

Topic selection	**Domain teams**	**Domain team work**				Final editorial work 2-3 months	Peer review and approval Process to be developed by WP4-5-8
		1st quarter	**2nd quarter**	**3rd quarter**	**4th quarter**		
	Editorial team	Finalize scope and protocol	Coordination	Coordination	Prepare for final editorial work		
	CUR						
	TEC						
	SAF						
	EFF						
	ECO						
	ETH						
	ORG						
	SOC						
	LEG						

This order of work takes into account the following key features of the process identified in previous projects:

- Results from the CUR, TEC and ORG domains are needed in several other domains.
- Work within CUR and TEC is closely related to scoping of the whole project.

- ECO domain needs input from EFF, CUR and ORG.
- ETH, SOC and LEG domains need input from several other domains.
- The Core HTA protocol needs to be agreed and locked for the subsequent phases to be functional within the HTA Core Model Online.

Bibliography

HTA Core Model Handbook (last version available)

2.2 Handling the electronic environment

Aim

The aim of this chapter is to provide guidance on the use of available EUnetHTA tools during the development of the project.

Evidence base

Several tools have been developed to facilitate the collaboration on the basis of the EUnetHTA JA1 experience.

Resources are available and include the HTA Core Model, POP database, Evident database. Intranet allows research teams to share documents and to exchange comments.

Training sessions are organised by Work package 2 and Work Package 8 to allow familiarization with different tools.

Practical guidance

The guidance in this chapter is limited to the use of tools at different steps of HTA information production.

Step 1- Topic notification

Consult the POP database to know if other organisations are working on the topic of interest or have planned to work on it to avoid duplication;

Step 2- Project planning

Project planning includes scoping, searching of information, formulating research questions, and planning methodologies. The objective of this phase is to develop a final Project Plan, including timelines, a list of all relevant questions to be answered and methodologies intended to be used in the assessment. The intranet should be used to share relevant documents on the topic. These can be useful in the scoping process. A Project Definition Template for core HTA is available in Appendix 7.

Instructions on the use of HTA Core Model Online can be found at
http://meka.thl.fi/htacore/ViewHandbook.aspx

Step 3- Assessment

The assessment involves finding answers to the questions of the protocol phase, the methodological guidance outputs for the HTA Core Model applications and this guidance. The objective of this phase is to produce HTA structured information to be included in result cards by each domain team.

To improve communication between teams draft documents should be shared in the intranet.

Step 4- Internal Review

Internal Review includes review of the assessment. The objective of this phase is to collect and address comments and suggestions for changes from dedicated reviewers.

Step 5 -External Review and Consultation/validation

External Review and Consultation includes consultation of the assessment with WP4 members, at least 1 clinical expert, the manufacturer(s) and other potential STKs (e.g. physicians, patients). The objective of this phase is to collect and address comments and opinions from all interested parties.

The Lead Partner (LP) will upload any useful documents on the intranet WP4 page to facilitate the exchanges among domain teams. Documents to be submitted to SAG consultation and to public consultation

will be uploaded also respectively in the Stakeholder Forum area of the EUnetHTA website and announced in the report page, in accordance with the EUnetHTA SOP.

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EVIDENT database: https://evident.has-sante.fr/has/login.xhtml

POP Database: http://eunethta.dimdi.de/PopDB/

2.3 National report production

Aim

The aim of this chapter is to provide an overview of the overall approaches that can be used to facilitate the use of the core HTA information for national report production.

Evidence base

A list of general toolkit resources (with hyperlinks) that can be consulted if further information and guidance is required on adaptation issues and transferability questions is at https://meka.thl.fi/htacore/Adaptation.aspx .

Practical guidance

Piloting of local/national reports using and producing Core HTA information has taken place during the Joint Action 2. Core HTA information is defined as “Any information on a technology that has been produced through using the HTA Core Model and published through the HTA Core Model Online”. 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.

There are three different approaches to national reporting activities:

1. To integrate Core HTAs information, already available from JA1/JA2, into national/local reports (Adaptation);
2. To produce both Core HTA information and national/local information on collaboratively prioritized topics (according to the procedure in par.1.4). The information is produced for joint and national reporting using EUnetHTA tools;
3. To produce both Core HTA information and national/local information using EUnetHTA tools on topics of national reporting interest.

The choice of an approach depends on the needs of each Organisation/Country and on the internal organization of work.

The following EUnetHTA tools were identified for each of the already mentioned approaches to facilitate national reporting.

Approaches	Basic Tools
1	Core HTAs, HTA collections *Adaptation (Toolkit & resources) available at* *https://meka.thl.fi/htacore/Adaptation.aspx*

2	HTA Core Model Application (for the selected topic) and Online Tool & Services (OT&S)
3	HTA Core Model Applications and Online Tool & Services (OT&S)

Approach 1:

The purpose of adaptation is to enable an HTA agency in one setting to make use of an HTA report (or Core HTAs and HTA collections) produced elsewhere, thus avoiding duplications and increase efficency. (https://meka.thl.fi/htacore/Adaptation.aspx). The extent to which this can be achieved depends on the generalizability of the topic under consideration and the different contexts in which it is to be considered.

The adaptation process could be undertaken in a wide range of ways, depending on the main purpose, and may range from simply translating the language in which the report is written, through to adapting the entire report:

1. Summarising: translate the summary and use this for background information.
2. Updating searches: using the original search strategy to identify any more recent evidence or adding to the search strategy and extending it.
3. Adapting: the systematic extraction of relevant HTA information from an existing report (from a whole report or from part of a report)
4. Adopting: making use of the report without making any changes at all (except perhaps translation into a destination language) (Chase et al., 2009; Turner et al., 2009)

Most safety and effectiveness evidence are context-independent for many health technologies and can be readily transferred to different contexts. However, specific attributes or acceptable trade-off levels may vary between contexts. Other heavily context dependent information, such as legal and ethical information, can't be readily adopted or easily adapted without significant appraisal in relation to the local context. (Chase et al., 2009)

A specific toolkit ("Adaptation Toolkit") was developed as part of Work Package 5 of the EUnetHTA 2006-2008 project. The final version is available on the EUnetHTA website (https://meka.thl.fi/htacore/Adaptation.aspx). The toolkit is a collection of resources that helps the user assess whether data and information in existing HTA reports should and could be adapted for their own setting (Turner et al., 2010).

Approach 2 and 3:

Approaches 2 and 3 are based on the production of both Core HTA information in the European context and in a national/local context.

The production of national/local information should be done after:

- checking the relevance of each assessment element at national/local level,
- identifying the assessment elements which are most likely to be transferable to other settings.

The elements within the HTA Core Model have been evaluated for two key characteristics: importance and transferability. In this context importance indicates how essential the element is from the view point of decision-making at national/local level. Transferability indicates how easy it is to transfer the results from one setting to another. All the other assessment elements partially or not transferable to local setting should be assessed from different national/local perspectives. However importance and transferability should be estimated from case to case.

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2.4 Carrying out evidence searches

Aim

To give guidance on how to construct, run, store and update searches

Evidence base

Readers should consult [EUnetHTA Guideline Process of information retrieval. Work on received comments from internal review, version for SAG / Public Cons. elaborated, start in FEB 2015]

Practical guidance

Below are three major issues to be considered based on *past experience* followed by *possible solutions* and at last a *suggested process.*

Past experience has shown that there is a need for a general evidence search using the standardized methods indicated in the guideline, as overlapping evidence searches within and across domains may led to duplication of work. Reference manager software should be used. To minimize duplications, the general search should be conducted centrally by an information specialist for all domains following a well-defined PICOD structure. Classic sources of information may however identify evidence for some domains (such as EFF, SAF and ECO) and other domains may need to supplement with searches of specialised sources such as books, specialist journals, government publications or surveys. Throughout the process the relevant questions contained in Assessment Elements should be borne in mind.

There is no agreed standard methodology for supplementary specialized searches. Primary Investigators (PIs) and Investigators (Is) of each domain should agree on a scope and methods to carry these out within a domain, if necessary (this includes analyzing, synthesizing and using critical appraisal tools). Any quality assessment of literature must be done by two independent researchers For detailed methodological support please refer also to updated HTA Core Model of WP 8 doc. using specific content suggestions where available.

Although several attempts have been made to eliminate duplication of specific evidence search due to *overlaps* of Assessment Elements (AE) within and across domains, there is no agreed methodology. One possible way to achieve this is for PIs of related overlapping domain questions to make contact and coordinate efforts along with the Project leader (PL) to avoid duplication of work. Please refer also to updated HTA Core Model applications on the EUnetHTA website .

Despite its practical importance (risk of reference loss, ease of communication, standardization, storage) there is no agreed reference manager software, although it would be strongly advisable to enable a uniform data management. We therefore suggest if available the use of a reference manager software compatible with other systems. As lack of coordination leading to duplication of searches is the most common practical pitfall so far identified, access to a standard process with clearly laid out rules and software aid is the best possible antidote to duplicate searches.

Bibliography

[EUnetHTA Guideline Process of information retrieval. Work on received comments from internal review, version for SAG / Public Cons. elaborated, start in FEB 2015]

Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]

Note for the next chapters: domain content may change over time, so readers are invited to check the latest version of the HTA core model.

2.5 Domain specific issues: Health problem and current use of technology (CUR)

Aim

The aim of this chapter is to describe the necessary information and the practical steps for the description of the "Health problem and Current Use of the Technology" for diagnostic technology (DT), screening technology (ST) and medical and surgical intervention (MST).

Evidence base

The following documents were used to define the practical guidance:

- EUnetHTA HTA Core Model Handbook (2012);
- EUNEHTA HTA Core Model For Screening Technologies (2012)
- EUnetHTA Assessment Element for Diagnostic Technologies (2012)
- EUnetHTA Assessment Element for Screening Technologies (2012)
- EUnetHTA Assessment Element for Medical and Surgical Interventions (2012)
- EUnetHTA Model for Rapid REA of pharmaceuticals (2013);
- Bossuyt et al. (2006);
- Newcastle-Ottawa Scale (Wells et al. 2008);
- STROBE checklist (von Elm et al. 2007)
- AGREE II instrument (Brouwers et al. 2010)

The guidance is structured as a table containing:

1. in the first column, labelled as "*Standard procedure\Data Source*", an assertive sentence for the action requested and sources for data retrieval are provided. If needed, details, suggestions and description of the most common pitfalls are provided.
2. a second column, labelled as "*References*", specifies the reference(s) at the basis of the action, where more details for accomplishing the procedure can be found.
3. a third column, labelled as "*Done*", to check if the action is done or not and why.

When different approaches and methodologies are needed, procedural steps are distinguished for each of the following type of technology: (1) Medical and Surgical Interventions (MST), (2) Diagnostic Technologies (DT), (3) Screening Technologies (ST). Unless otherwise specified, the procedural step is to be considered applicable for all three types of technology.

Practical guidance

The operational steps for compiling the "Health problem and current use of technology" are:

1. select the topics from the EUnetHTA HTA Core Model (8 Apr 2014 version)
2. search the information in the data sources
3. assess the quality of the information retrieved
4. apply the instruments for the analysis and synthesis
5. report the results

Readers should be aware that earlier versions of the HTA Core Model Handbook contained links to the actual guidance within the Model. The links were removed and in some cases it was difficult for users to identify the actual source of guidance. Please consult individual model applications for the actual guidance, available at www.corehta.info.

293 ***1.1. Selection of the topics/issue and search of information***

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Standard procedure and Data sources	References	Done (Yes, No, because…)
Select the topics and issues from the HTA Core Model Assessment Elements The topics related to Health problem and Current Use of the Technology are in the EUnetHTA Assessment Element with Identification number from A0001 to A0022	EUnetHTA HTA Core Model Handbook (2014) EUnetHTA Assessment Element for Diagnostic Technologies (2014) EUnetHTA Assessment Element for Screening Technologies (2014) EUnetHTA Assessment Element for Medical and	
Describe the target condition: *disease mechanisms , natural course of condition, burden, prevalence and incidence of the condition, risk factors and consequences, diagnosis and prognosis, target population* Search this information in published medical literature, clinical practice guidelines, reviews on mechanism of disease, risk factors, course and prognosis, epidemiological studies such as Cross-Sectional Studies (Prevalence), Cohort-Studies (Incidence) ***Data source*** - *HTAs, systematic reviews and original research can be found in Cochrane Database of Systematic Reviews and Cochrane CENTRAL, Centre for Reviews and Dissemination (CRD), Medline, Embase, Cinahl, PsycINFO.* - *Evidence-based guidelines can be found in reference databases, guidelines producers' websites and in Guidelines International Network's (GIN) website.* - *Websites of health technology assessment agencies* - *Registers and statistics* *Disease registers* *Administrative Databases (discharge databases, reimbursement claims*	EUnetHTA Assessment Element for Diagnostic Technologies (2014) EUnetHTA Assessment Element for Screening Technologies (2014) EUnetHTA Assessment Element for Medical and Surgical Interventions (2014) Model for Rapid REA of pharmaceuticals 2013. Table 1. Health problem and current use of technology Domain specific sources	

Describe the Current Management of the Condition**:** *how is the disease/health condition currently being diagnosed or screened, how is the disease/health condition currently being managed, how should the condition be diagnosed according to published algorithms/guidelines, how should the condition be managed according to published algorithms/guidelines, what are the differences in the management for different stages of disease and what are the other evidence-based alternatives to the current technology.* ***Data source*** - *Evidence-based guidelines can be found in reference databases, guidelines producers' websites and in Guidelines International Network's (GIN) website* - *Specialists or experts consultation* - *Expert surveys or interviews*	EUnetHTA Assessment Element for Diagnostic Technologies (2014) EUnetHTA Assessment Element for Screening Technologies (2014) EUnetHTA Assessment Element for Medical and Surgical Interventions (2014) Model for Rapid REA of pharmaceuticals 2013. Table 1.(HPCU) Domain specific sources	
Describe the utilization of the technology: *how much is the technology being used and the variations in use across countries/regions/settings.* ***For Screening Technologies (ST) describe the current rate of screening adherence*** ***Data source*** - *Disease Registers* - *Technology Registers* - *Procedure Registers* - *Device registers* - *Administrative Databases (discharge databases, reimbursement claims databases)*	EUnetHTA Assessment Element for Diagnostic Technologies (2014) EUnetHTA Assessment Element for Screening Technologies (2014) EUnetHTA Assessment Element for Medical and Surgical Interventions (2014) Model for Rapid REA of pharmaceuticals 2013. Table 1.(HPCU) Domain specific sources	
Describe the Life-Cycle of the technology: *in which phase is the development of the technology (experimental,emerging, routine use, obsolete)* ***Data source*** - *Horizon scanning databases and websites* - *Ongoing research databases* - *Technology developers and manufacturers websites* - *ECRI database(www.mdsr.ecri.org)*	EUnetHTA Assessment Element for Diagnostic Technologies (2014) EUnetHTA Assessment Element for Screening Technologies (2014) EUnetHTA Assessment Element for Medical and Surgical Interventions (2014) Model for Rapid REA of pharmaceuticals 2013. Table 1.(HPCU) Domain specific	

Describe the regulatory status of the technology: *which approval status has the technology in other countries (e.g. USA) or international authorities and how is the coverage of the technology across counties* *N.B.: European Directives differentiate between In Vitro Diagnostic Medical Device (Directive 98\79\EC), active implantable medical devices (Directive 90\385 EEC) and (other) medical devices (Directive 93\42\EEC)* *The Directive 2007\47\EC introduced the obligation for the Commission to implement Eudamed, which at present is still in progress.* Data source - *Manufacturers* - *Marketing authorisation and other regulatory institutions' websites e.g. (Europe: EMA; US: FDA; Canada: Health Canada; New Zealand: MedSafe; Australia: TGA)* - *National health services' websites* - *Regional/local governments' health departments' websites*	EUnetHTA Assessment Element for Diagnostic Technologies (2014) EUnetHTA Assessment Element for Screening Technologies (2014) EUnetHTA Assessment Element for Medical and Surgical Interventions (2014) Model for Rapid REA of pharmaceuticals 2013. Table 1.(HPCU) Domain specific sources	

1.2. Quality assessment tools or criteria

In the second column of the table are reported the characteristics of studies and data sources for the description of the different elements.

Standard procedure	**Study type/data sources**	**References**	**Done** **(Yes, No because)**
To evaluate the quality of studies on ***disease mechanisms****, no tools are provided*	*Descriptive*	HTA Core Model For Screening Technologies (2014)	
To evaluate the quality of ***Natural course of condition*** *studies the STROBE checklist or Newcastle-Ottawa Scale can be used*	*Observational*	HTA Core Model For Screening Technologies (2014) STROBE checklist (von Elm et al. 2007)	
To evaluate the quality of ***Burden of disease, prevalence and incidence of the condition*** *studies the STROBE checklist or Newcastle-Ottawa Scale can be used*	*Observational*	HTA Core Model For Screening Technologies (2014) STROBE checklist (von Elm et al. 2007)	

To evaluate the quality of **Risk factors and consequences** *studies the STROBE checklist or Newcastle-Ottawa Scale can be used*	*Observational*	HTA Core Model For Screening Technologies (2014) STROBE checklist (von Elm et al. 2007) Newcastle-Ottawa Scale (Wells et al. 2008)	
To evaluate the quality of ***Target population*** *studies, no tools are provided* *To evaluate the quality of* ***data*** *for* ***Target population*** *you have to distinguish:* ***for Registers - quality*** *should be appraised carefully considering the following questions:* • *How representative is the register? (European, National, Regional, Local?)* • *What are the inclusion/exclusion criteria?* • *What is the quality of information?* • *How complete is the coverage?* • *What kind of information is coded?* • ***for Routine collected statistics and administrative data*** *you must take into account that 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 is known to be very limited.*	*Narrative review, scientific associations guidelines recommendations* *Register analysis, routine collected statistics and administrative data*	*Not needed*	
To evaluate the quality of ***data*** *for* ***Utilization of technology*** *considerations made in the above paragraph apply.*	*Narrative reviews,* *surveys,* *observational and*		

	qualitative research, *register analysis, routine collected statistics and administrative data*		
*To evaluate the quality of guidelines for **Current Management of the Condition** AGREE II tools will be used* *The evaluation of the quality of data sources for **Current Management of the Condition** is not provided*	*Clinical guidelines* *Information from websites of relevant associations of health care professionals or disease-specific societies*		
*To evaluate the quality of data for **Life-Cycle of the technology*** *you must take into account that potential bias in the information provided by manufacturers needs to be carefully assessed*	*Manufacturers*		
*To evaluate the quality of data for **regulatory status** (approval status) you must take into account that potential bias in the information provided by manufacturers needs to be carefully assessed*	*Marketing authorisation and other regulatory institutions' websites e.g. Manufacturers*		

1.3. Analysis and synthesis

The type of synthesis suggested is reported in the second column

Standard procedure	**Type of Synthesis**	**References**	**Done (Yes, No because)**
Synthesis *of information on **Disease mechanisms***	Narrative	HTA Core Model For Screening Technologies (2014)	
Synthesis *of information on **Natural course of condition***	Narrative	HTA Core Model For Screening Technologies (2014)	
Synthesis *of information on **burden, prevalence and incidence of the condition***	Data may be meta-analysed, but often there is no opportunity to do that	HTA Core Model For Screening Technologies (2014)	

Synthesis *of information on* ***Risk factors and consequences***	Meta-analysis per subgroups if possible	HTA Core Model For Screening Technologies (2014)	
Synthesis *of information on* ***Target population***	Narrative	HTA Core Model For Screening Technologies (2014)	
Synthesis *of information on* ***Utilization of technology***	Narrative	HTA Core Model For Screening Technologies (2014)	
Synthesis *of information on* ***Current Management of the Condition***	Narrative	HTA Core Model For Screening Technologies (2014)	
Synthesis *of information on* ***Life-Cycle of the technology***	Narrative	HTA Core Model For Screening Technologies (2014)	
Synthesis *of information on* ***regulatory status of the technology***	Narrative	HTA Core Model For Screening Technologies (2014)	

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304 **1.4. Reporting**

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Standard procedure	**Reference**	**Done (Yes, No because)**
For all topics • *check relations to other domains to ensure coherence* • *Define important terms in a glossary* • *Check that the sources of information used explicitly be documented*	HTA Core Model Handbook (2014)	
For the target condition *Check that the Disease mechanisms, natural course of condition, Burden, prevalence and incidence of the condition, Risk factors and consequences and target population are analysed*		

and syntheses as 3.3		
For the utilization of technology *Check that European level and national data with abundant numerical information through tables, graphs and figures are reported*	HTA Core Model For Screening Technologies (2014)	
For the Current Management of the Condition *Check that an illustrative synthesis is reported. Flowchart of current management pathway is particularly illustrative in diagnostic technology and helps the reader to understand the intended role of the new technology (replace, add-on ,triage).*	HTA Core Model For Screening Technologies (2014) Bossuyt et al. (2006);	
For the Life-Cycle of the technology *check that illustrative synthesis is reported*		
For the regulatory status *Check that the regulatory status are reported*		

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320 Online Tool) . Available at http://www.eunethta.eu/outputs/final-hta-core-model-screening-technologies ; last
321 access Febrary 13th 2015.

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326 current features of the Online Tool) Available at https://meka.thl.fi/htacore/ViewHandbook.aspx?full=1&id=6
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2.6 Domain specific issues: Description and technical characteristics of technology (TEC)

Aim

The aim of the methodological guidance for the TEC domain is to provide HTA Core Model users with a brief list of issues on the description and technical characteristics of the technology which have to be taken into account when answering the relevant assessment elements, and, thus, guide them through a step-by-step procedure which will facilitate quality.

Evidence base

The evidence base, applied methods, and information sources are described under chapter 2 Practical guidance.

Practical guidance

Information sources

A. Systematic search

Did you check published literature including reviews, introduction sections of research articles, conference proceedings, textbooks or handbooks about the history and characteristics of the technology? Examples of sources: ➢ Medline/Pubmed http://www.ncbi.nlm.nih.gov/pubmed ➢ Embase ➢ Cochrane Library http://www.thecochranelibrary.com/view/0/index.html ➢ EBSCO http://www.ebsco.com/index.asp ➢ Centre for Reviews and Dissemination (CRD) http://www.york.ac.uk/inst/crd/ ➢ BIOSIS (life sciences database including patents, journals, conferences, books, review articles (http://science.thomsonreuters.com/training/biosis)	Yes	No, because …
Did you check the reference lists of key papers?		

B. Hand search

Did you search for national guidelines concerning the application of the technology? Examples of sources: ➢ Guidelines International Network (GIN) http://www.g-i-n.net/ ➢ National Clinical Guideline Center http://www.ncgc.ac.uk/ ➢ National Guideline Clearinghouse http://guideline.gov/index.aspx	Yes	No, because …
Did you search for grey literature to find out more about the technology (e.g. technical reports from government agencies or scientific research groups, working papers from research groups or committees, white papers, or preprints)?	Yes	No, because …
Did you contact manufacturers or search for information about the technology on manufacturers' websites?	Yes	No, because …
Did you search for information on the websites of HTA and related agencies or professional associations to find out about the technology? Examples of sources:	Yes	No, because …

➢ Websites from EUnetHTA members ➢ HTAi (http://www.htai.org) ➢ Health technology assessment on the net' report (http://www.ahfmr.ab.ca) ➢ International network of agencies for HTA http://www.inahta.net/		
Did you check if the technology has obtained regulatory approval and did you list it in the Core HTA? Examples of sources: ➢ EU or US regulatory bodies ➢ regulatory bodies in those countries where the technology has been approved for use		

352 C. **Survey or Interviews**

Did you use a questionnaire to get information about technical aspects of the technology?	Yes	No, because …
Did you interview specialists or experts concerning the technology (e.g. clinicians, nurses, paramedics, patients)?	Yes	No, because …

353 D. **Quality assessment tools or criteria**

Did you use peer reviewed literature when possible?	Yes	No, because …
Did you describe how you assessed the quality of the included information?	Yes	No, because …

354 E. **Analysis and synthesis**

Are the findings referred to sources explained clearly in order to enhance the transparency of the Core HTA?	Yes	No, because …

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356 F. **Reporting**

Did you check relations of TEC to other domains (CUR, ORG, LEG) to avoid double work?	Yes	No, because …
Are the approaches and sources of information used explicitly documented in the Core HTA?	Yes	No, because …
Did you describe the design and function of the technology sufficiently for the users of HTA 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?	Yes	No, because …
Did you describe the issues in this domain detailed enough in order to separate the technology in question from related technologies?	Yes	No, because …
For medical devices: Did you include drawings or schematics for the technology that illustrate the components, dimensions and materials of construction of the device?	Yes	No, because …
For diagnostic and monitoring technologies (laboratory tests, imaging, questionnaires etc): Did you include sufficient information about the technical precision of the technology?	Yes	No, because …

For management processes (such as screening programs): Did you describe the position and interaction of the technology within the broader healthcare sequence and did you list alternative technologies?	Yes	No, because …
Did you list the product names of the technology?	Yes	No, because …
Did you define important terms in a glossary?	Yes	No, because …

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358 **Bibliography**

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2.7 Domain specific issues: Safety of the technology (SAF)

Aim

The aim of this guidance is to describe the necessary information and practical procedures and steps for the production of the Assessment Elements for the Core HTA's Safety domain.

Evidence base

The following procedural framework was applied: firstly, methodological deliverables by EUnetHTA were included and consulted in order to design the structure for a comprehensive review on the safety of the technology in object. Then, handbooks or manuals for producing systematic reviews from institutions contributing to the methodology of systematic reviews were non-systematically consulted from specific websites and included. Finally, tools and methods for single specific procedural steps were non-systematically searched and included. The documents included were compared for consistency.

The following documents were used in order to define the general design for the practical guidance of procedures:

- Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011);
- CRD's Guidance for Undertaking Reviews in Healthcare (Centre for Reviews and Dissemination 2009);
- HTA Core Model Handbook (2012);
- HTA Core Model Update 1.5, 8 Apr 2014
- EUnetHTA Model for Rapid REA of pharmaceuticals (2013);
- EUnetHTA Guideline: Endpoints used for REA of pharmaceuticals – Safety (2013)
- EUnetHTA Guideline: Methodological guideline for REA of pharmaceuticals: Internal validity (2013)

In addition to the above documents, the followings were used to define single procedural steps:

- AHRQ Methods Guide for Medical Test Reviews (2012);
- AHRQ User's guide - Registries for evaluating patient's outcomes (Gliklich et al .2010)
- AMSTAR instrument (Shea et al. 2007);
- CONSORT Statement (Ioannidis et al. 2004);
- EUnetHTA Assessment Element for Diagnostic Technologies (2012);
- EUnetHTA Assessment Element for Screening Technologies (2012);
- EUnetHTA Assessment Element for Medical and Surgical Interventions (2012);
- HTA Core Model on Abdominal Aorta Aneurysm Screening (Jefferson et al. 2013a);
- HTA Core Model on Prognostic tests for breast cancer recurrence (uPA/PAI-1 [FEMTELLE], MammaPrint, Oncotype DX) (Jefferson et al. 2013b);

- GRADE method (Balshem et al. 2011, Guyatt et al. 2011a, Guyatt et al. 2011b, Guyatt et al. 2011c, Guyatt et al. 2011d, Guyatt et al. 2011e, Guyatt et al. 2011f, Guyatt et al. 2011g, Guyatt et al. 2013, Schünemann et al. 2008);
- Newcastle-Ottawa Scale (Wells et al. 2008);
- PRISMA Statement (Moher et al. 2009);
- STROBE Statement (von Elm et al. 2007)
- GL Internal validity of non-randomised studies (NRS) on interventions: internal consultation of draft guideline finalised (16th of JAN 2015) , work on comments and preparation of version for SAG / Public Cons.

The guidance is structured as a table containing:

1. a first column with an assertive sentence for the action requested, labelled as "*Standard procedure*". If needed, details, suggestions and description of the most common pitfalls are provided.
2. a second column, labelled as "*References*", specifying the reference(s) at the basis of the action, where more details for accomplishing the procedure can be found.
3. a third column, labelled as "*Done*", to check if each action has been completed or not and why.

If different approaches and methodologies are needed, every procedural step is distinguished for each of the following types of technology: (1) Medical and Surgical Interventions, (2) Diagnostic Technologies, (3) Screening Technologies, (4) Prognostic Technologies. Unless otherwise specified, the procedural step is to be considered applicable for all four types of technology.

Practical guidance

In this chapter the procedural steps needed to produce the Assessment Elements for the Safety domain are reported.

According to the HTA Core Model Handbook (2012), in order to assess the safety of a technology a systematic approach is required. However it is also recognised that the definitions and the terminology of safety used in HTA have not been standardised so far and a multiplicity of terms are used, such as side-effects, adverse events, adverse effects, complications, harms, risks and hazards, safety, tolerability and toxicity (Ioannidis 2004).

The wide scope of identifying and assessing all possible harms caused through the use of a technology, requires a focus on three different sub-categories of safety:

1. risks or possible injuries, accidents and losses patients may be exposed to, due to the use of the technology; for instance excessive radiation, technology or system failure. These outcomes are usually investigated in Phase I and II trials, when evaluating drugs, or in feasibility studies or studies on technical performance, when evaluating medical devices;

2. adverse events and adverse side effects related to the use of the technology, taken into consideration to counterbalance the evaluation of the technology's benefits. These outcomes are best investigated through Phase III or comparative effectiveness clinical trials;

3. long-term adverse events and rare adverse effects related to the prolonged and wide use of a technology, which presents a favourable balance between evaluated benefits and harms. These outcomes are best investigated with Phase IV trials, surveillance and large observational long-term studies.

In HTA "the aim is not necessarily to cover all known and previously unrecognised harms of a technology (…) rather, Core HTA preparers should focus their review and predefine the safety issues and outcome measures they wish to work in their assessment".

Every aspect has different safety objectives, endpoints and different methodology and tools to assess them. In order to harmonize the HTA Core Model work among different domains (namely TEC, SAF, EFF) we recognize that the safety assessment could be either entirely completed in this SAF domain or split among the TEC, SAF, and EFF domains.

In particular issues related to the risks carried by the developmental phase of a technology need to be incorporated in the TEC domain; adverse events and side effects determining the overall "clinical impact" of the technology should be part of the EFF domain, while long term/rare and unknown adverse events of a technology which has passed the scrutiny of effectiveness, i.e data from the "vigilance phase", should be specifically addressed in the SAF domain.

It is reviewers' responsibility to choose the best approach for accomplishing the goal.

To complete the Assessment Elements for the Safety domain, comprehensive reviews or systematic reviews, answering each selected issue, need to be carried out. To accomplish these goals the following steps are considered (CRD's Guidance for Undertaking Reviews in Healthcare 2009, Higgins et al. 2011, HTA Core Model Handbook ver 1.5, 8 Apr 2014, HTA Model for Rapid REA of pharmaceuticals 2013, Moher et al. 2009):

3.1 Definition of the relationship of the SAF domain with TEC and EFF domains
3.2 Selection of the topics and issues from the HTA Core Model Assessment Elements
3.3 Definition of research questions
3.4.Definition of inclusion criteria for considering studies
3.5 Systematic search of evidence
3.6 Selection of the studies
3.7.Data extraction
3.8.Methodological quality assessment
3.9.Data synthesis
3.10 Grading of quality of evidence
3.11 Reporting

3.1 Definition of the relationship of the SAF domain with TEC and EFF domains

Standard procedure	References	Done

Establish whether the whole aspects of safety will be assessed in the SAF domain or split between TECH, EFF and SAF domains	• Safety domain, HTA Core Model Update 2013 (draft version 27th June, 2013)	Yes No (explain)

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476 **3.2 Selection of the topics and issues from the HTA Core Model Assessment Elements**

Standard procedure	References	Done
Select the topics and issues from the HTA Core Model Assessment Elements	• Chapter 2.2.2 Phase 2: Protocol design, in HTA Core Model Handbook (2014) • Assessment Element for Diagnostic Technologies (2014) • Assessment Element for Screening Technologies (2014) • Assessment Element for Medical and Surgical Interventions (2014) • Chapter 3.3. Safety, in HTA Core Model Handbook (2014)	Yes No (explain)
Core HTA authors, who are not aware of any specific safety problem, could start with a broad overview of the whole range of adverse effects associated with the use of the technology.	• Chapter 3.3. Safety, in HTA Core Model Handbook (2014)	Yes No (explain)
If you have to assess a prognostic technology refer to guidance for diagnostic technologies *N.B.: Methods specific to conduct a systematic review of a prognostic test are not well established. Currently there are only three applications of the HTA Core Model: medical and surgical interventions, diagnostic technologies, and screening technologies. While awaiting for specific methodological guidance on prognostic technologies, refer to guidance for diagnostic technologies. However, there are fundamental differences in the assessment of diagnostic and prognostic tests, thus consider that HTA Core assessment element questions for diagnostic technologies are thus not suited for prognostic technologies.*	• Clinical Effectiveness, Methodology Description Chapter, in HTA Core Model on Prognostic tests for breast cancer recurrence (Jefferson et al. 2013b) • Chapter 12. Systematic Review of Prognostic Tests, in Methods Guide for Medical Test Reviews (AHRQ 2012)	

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478 **3.3 Definition of research questions**

Standard procedure	References	Done
Define research question(s) according to the PICOD system PICOD stands for participants, interventions, comparisons, outcomes, and study design.	• Chapter 2.2.4, Phase 4: Protocol design, in HTA Core Model Handbook (2014) • Appendix 3, Systematic review of the literature, in Model for Rapid REA of pharmaceuticals 2013. • PRISMA Statement (Moher et al. 2009)	Yes No (explain)
Anticipate and choose if it is necessary or not to cover all known and unrecognised harms of a technology *N.B.:* 1. *Systematic assessment of all safety issues of a technology can be time consuming. It might be reasonable for authors of a Core HTA to 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. Thus the aim is not necessarily to cover all known and previously unrecognised harms of a technology. Rather, Core HTA preparers should focus their review and predefine the safety issues and outcome measures they wish to work in their assessment.* 2. *Core HTA authors may choose to narrow down into some of the following areas:* a. *the five to ten most frequent adverse effects* b. *all adverse effects that either the patient or the clinician considers to be serious* c. *the most common adverse effects that lead the patient to stop using the intervention* d. *by category (for example: diagnosed by clinician, diagnosed by lab results, patient-reported symptoms, biomarkers that may be early indicators of possible adverse effects* e. *consider also patients' exclusion criteria in effectiveness trials, which might reveal/mask expected adverse events.*	• Chapter 3.3. Safety, in HTA Core Model Handbook (2014)	Yes No (explain)
Be aware that several harm categories may help identifying and classifying research questions for the safety domain and relations to other domains. Harms should classified according to intensity, frequency, on set timing, seriousness and severity. Seriousness is classified as mild, moderate and serious. Serious refers to adverse effects that have	• Chapter 3.3. Safety, in HTA Core Model Handbook (ver 1.5, 8 Apr 2014) • Safety domain, HTA Core Model Update 2014	Yes No (explain)

significant medical consequences (e.g. lead to death, permanent disability or prolonged hospitalisation). Severity 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 following categories, can be considered in relation to the TEC domain as they describe the direct harms of the use and the administration of the technology: • direct harm (due to e.g. radiation, toxicity or invasiveness) or indirect harm (due to e.g. insufficient training, experience, maintenance, diagnostic error) • operator or setting dependent harms (e.g. they can be modified by changing practices or affecting users´ knowledge, skills and behaviour) or patient dependent harms (e.g. which means that there are vulnerable patient groups in whom protection is especially required) • occupational harms and environment harms • possible variations in the safety profile between different generations/versions of the technology • besides patients, the use of a technology may cause harm to their family and close ones, health care professionals, public, and the environment. The following categories, can be considered in relation to the EFF domain as they describe adverse effects / events directly or indirectly attributable to the use of the technology and which must be considered when evaluating balance between benefits and harms: • intended or unintended harms • dose-related harms or time-relatedness harms, tolerability, toxicity • negative consequences of false test's results and of further testing and treatments/delay in treatment in patients with false test's results The following categories, can be considered specific to the SAF domain as they relate to late and rare adverse events: • unexpected harms and late adverse reactions • misuse and abuse of the technology		
Adopt standardised definitions and terminology of harms	• Chapter 3.3. Safety, in HTA Core Model Handbook (2014)	Yes

N.B.: o *The definitions and the terminology of safety used in HTA have not been standardised. A number of initiatives aim to harmonise safety terms. Examples include the National Cancer Institute Common Terminology Criteria for Adverse Events, the WHO Adverse Reaction Terminology, the Medical Dictionary for Regulatory Activities (MedDRA) Terminology.* o *Core HTA authors can use any terms they find proper. However the Model for Rapid REA of pharmaceuticals (2013) recommends the use of MedDRA for describing adverse reactions.* o *Be aware that the standard 'preferred terms' in some cases can distort descriptions in the original reports of adverse events and blur distinctions between them.*	• Safety domain, HTA Core Model Update 2014 (version 1.5, 8 Apr 2014) • Appendix 5, Recommendations of guidelines on methodological issues, Safety, in Model for Rapid REA of pharmaceuticals 2013. • Common Terminology Criteria for Adverse Events (CTEP, National Cancer Institute) • WHO Adverse Reaction Terminology (WHO-ART, Uppsala Monitoring Center) • Medical Dictionary for Regulatory Activities Terminology (MedDRA, MSSO)	No (explain)

3.4 Definition of inclusion criteria for considering studies

Standard procedure	References	Done
Define “Criteria for considering studies for inclusion” according to elements of PICOD.	• Chapter 5, Defining the review question and developing criteria for including studies, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011)	Yes No (explain)
The inclusion criteria must be established for the following elements: - Population/patient characteristics - Types of interventions - Types of comparators - Relevant safety outcomes - Study design - Publication type - Publication date - Language *N.B.: for this procedure you must take into account that* 1) *Depending on the novelty of the technology you should evaluate whether you include only studies published in peer-review studies or if you will also take into account information from conference abstracts, unpublished data.* 2) *Inclusion/Exclusion criteria should be clearly*	• Chapter 14, Systematic reviews of adverse effects, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • Chapter 2, Methods, in Model for Rapid REA of pharmaceuticals (2013) • Chapter 14, Adverse effects, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011) • Chapter 13, Including non-randomized studies, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011)	Yes No (explain)

presented in the report		
You may need to consider a broad range of study designs for the systematic assessment of Safety *N.B.: although safety data from RCTs are considered most reliable, the inclusion of data from sources with higher risk of bias may be necessary when RCTS are scarce, harms are unknown, rare, or occurring only during long follow-up. These may include observational studies, country registers and published case reports.*	• Chapter 2.5.1, Appropriate study types, in Model for Rapid REA of pharmaceuticals (2013) • Chapter 3.3. Safety, in HTA Core Model Handbook (2012) • Chapter 14, Systematic reviews of adverse effects, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • Chapter 14, Adverse effects, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011)	Yes No (explain)

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482 **3.5 Systematic search of evidence**

Standard procedure	References	Done
To identify evidence on harms you need to search several and diverse/different sources. Thus conduct a comprehensive systematic search of evidence: - General medical databases *N.B.: Be aware that for general medical databases there is no optimal search strategy to specifically identify reports of adverse effects. Combination of different approaches in Medline and Embase is needed. New, previously unrecognised remain easily undetected and several study types should be considered for inclusion in the search.* - Systematic review databases/HTA databases - Primary sources of unpublished information or data, such as: manufacturers product data sheets or application for a product license; national or international safety monitoring systems/databases of adverse events; disease or technologies registries; pharmacovigilance systems or spontaneous adverse events databases; routine statistics from hospital, primary care, health system founders; specific enquiries to manufacturers, regulators or professional bodies.	• EUnetHTA Guideline: Methodological guidelines for rapid relative effectiveness assessment (REA) of Pharmaceuticals developed in WP5 of EUnetHTA JA: Safety (2013) • Chapter 3.3. Safety, in HTA Core Model Handbook (2014) • Safety domain, HTA Core Model Update 2013 (version 1.5, 8 Apr 2014) • Appendix 3, Systematic review of the literature, in Model for Rapid REA of pharmaceuticals 2013. • Appendix 5, Recommendations of guidelines on methodological issues, Safety, in Model for Rapid REA of pharmaceuticals 2013. • Chapter 4, Systematic reviews of adverse effects, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • Chapter 14, Adverse effects, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al.	Yes No (explain)

	2011)	
For each search draft a sufficiently detailed report of searches and databases should be provided to allow the search to be reproduced. The process should be explicitly defined including search strategy. A flow chart with number of studies retrieved, studies included and excluded and reasons for exclusion is recommended. You should update the search at the end of the review	• [EUnetHTA Guideline Process of information retrieval. Work on received comments from internal review, version for SAG / Public Cons. elaborated, start in FEB 2015] • Appendix 3, Systematic review of the literature, in Model for Rapid REA of pharmaceuticals (2013) • Chapter 6, Searching for studies, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011)	Yes No (explain)
Use bibliographic software to manage references.		Yes No (explain)

3.6 Selection of the studies

Standard procedure	References	Done
Perform the selection of studies through the following steps: - selection of potentially relevant titles and /or abstracts and retrieval of full-texts - assessment of full papers considered as potentially relevant - inclusion of the final set of studies *N.B.: for this procedure you must take into account that* *1) Assessment of eligibility of studies, and extraction of data from study reports, should be done by at least two people, independently* *Studies, rather than publications, are the unit of interest of the review, therefore multiple publications of the same study need to be linked together. Duplicated studies should be eliminated.*	• Appendix 3, Systematic review of the literature, in Model for Rapid REA of pharmaceuticals (2013) • Chapter 7, Selecting studies and collecting data, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011) • Chapter 1, Core principles and methods for conducting a systematic review of health interventions, in CRD's Guidance for Undertaking Reviews in Healthcare (2009)	Yes No (explain)

3.7 Data extraction

Standard procedure	References	Done
Define all data you have to collect and design a standardized data collection form. Data extraction should include frequency,	• Chapter 3.3. Safety, in HTA Core Model Handbook (2012) • Chapter 4, Systematic reviews of	Yes No (explain)

severity, seriousness of the event and withdrawals from treatment because of adverse events and for unknown reasons.	adverse effects, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • Chapter 7, Selecting studies and collecting data, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011) • Template 5, Table for reporting results from clinical trials, in Model for Rapid REA of pharmaceuticals (2013)	
Describe how the data extraction process is to be performed in terms of - the data categories and information requirements that are to be collected - how verification of extracted data from each report will be verified (e.g. extraction by two review authors, independently) - piloting, training and existence of coding instructions for the data collection form; - how data are extracted from multiple reports of the same study - how disagreements are handled if more than one author extracts data from each report *N.B.: for this procedure you must take into account that when you design the data extraction form you should take into account the aim of the report, research questions but also the information that will be relevant for quality assessment and analysis of results*		Yes No (explain)

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488 **3.8 Methodological quality assessment**

Standard procedure	References	Done
Assess both the risk of bias of sources of information and the quality of data on adverse reactions	• Appendix 5, Recommendations of guidelines on methodological issues, Safety, in Model for Rapid REA of pharmaceuticals 2013.	
Assess the risk of bias considering the specificity of each study design and source of data, and, if appropriate, using validated frameworks and tools for the methodological quality/risk of bias/internal validity. *N.B.: for this procedure you must take into account that* *1) there is a lack of a relevant quality assessment tool to appraise evidence on harms. Any available tool should be used cautiously. Comparing evidence from randomised trials and observational studies is useful* *2) you must apply different tools for*	• Chapter 3.3. Safety, in HTA Core Model Handbook (2012) • Safety domain, HTA Core Model Update 2013 (draft version 27th June, 2013) • Appendix 5, Recommendations of guidelines on methodological issues, Safety, in Model for Rapid REA of pharmaceuticals 2013. • Chapter 4, Systematic reviews of adverse effects, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • Chapter 8, Assessing risk of bias in included studies, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011) • Chapter 13, Including non-randomized studies, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011)	Yes No (explain)

different study scope *3) there is currently no consensus on how to incorporate information about quality from a range of study designs within a systematic review*	• Chapter 14, Adverse effects, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011)	
However relevant questions in order to assess the quality of adverse effects data are suggested by some institutions. CRD: • Is there an adequate explanation of how adverse effects were identified? • Was a standardised or validated measurement instrument used? • How was the adverse effect(s) attributed to the intervention? • Are the terms clearly explained? EUnetHTA (HTA Core Model 2012) • How rigorous were the methods used to detect adverse effects? Were the methods used for monitoring reported? • Was follow up sufficiently long to assess the risk for serious longer term safety issues? • How complete is the reporting? Did the investigators report all important or serious harms? Did the report give numerical data by group? • How were data collected: prospective/routine monitoring, spontaneous reporting, patient checklist/questionnaire/diary; systematic survey of patients? • Were any patients excluded from the harms analysis? EUnetHTA (HTA Core Model Update 2014, draft) • Were the methods used for detecting adverse effects reported: prospective or routine monitoring, spontaneous reporting, or patient checklists/questionnaires/diaries ? • How rigorous were these methods?	• Chapter 4, Systematic reviews of adverse effects, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • Chapter 3.3. Safety, in HTA Core Model Handbook (2014) • Safety domain, HTA Core Model Update 2013 (draft version 8 April 2014) • Appendix 5, Recommendations of guidelines on methodological issues, Safety, in Model for Rapid REA of pharmaceuticals 2013.	

• Was the follow-up sufficiently long to assess the risk for serious longer term safety issues? • How complete is the reporting? Did the investigators report all serious or common harms? • Did the report give numerical data by group? • Were any patients excluded from the harms analysis? EUnetHTA (REA 2013) Useful questions to assess how the adverse reactions are collected: • Were definitions given of reported adverse effects? • How were adverse effects data collected: prospective/routine monitoring, spontaneous reporting, patient checklist/ questionnaire/diary; systematic survey of patients? Useful questions to assess how the adverse effects are reported: • Were any patients excluded from the adverse effects analysis? • Did the report give numerical data by intervention group? • Which categories of adverse effects did the investigators report? • Did investigators report on all important or serious adverse effects, and how were these defined? • Were methods used for monitoring adverse effects reported? • Was an independent data safety monitoring board established?		
To assess methodological quality/risk of bias/internal validity of systematic reviews you could refer to the AMSTAR instrument or to the NOKC checklist for systematic reviews	• Shea et al. 2007 • Appendix EFF-1 Section 4, in Abdominal Aorta Aneurysm Screening (Jefferson et al. 2013a)	Yes No (explain)
To assess methodological quality/risk of bias/internal validity of RCTs you could	• Chapter 14, Adverse effects, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011)	Yes No

refer to the risk of bias system proposed by the Cochrane Handbook for Systematic Reviews of Interventions or to the extension of the CONSORT statement: for better reporting in randomised trials	• Chapter 8, Assessing risk of bias in included studies, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011) • CONSORT statement (Ioannidis 2004)	(explain)
To assess methodological quality/risk of bias/internal validity of cohort studies you could refer to the Newcastle-Ottawa Scale or to the STROBE Statement	• Chapter 14, Adverse effects, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011) • Cochrane Handbook for Systematic Reviews of Interventions 2011. Chapter 13: Including non-randomized studies • Wells et al. 2008 • von Elm et al. 2007	Yes No (explain)
To assess methodological quality/risk of bias/internal validity of case reports you could refer to issues proposed by the Cochrane Collaboration	• Chapter 14, Adverse effects, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011)	Yes No (explain)
To evaluate the quality of Registers you must take into account that the quality of registers should be appraised carefully considering the following questions: • How representative is the register? (European, National, Regional, Local?) • What are the inclusion/exclusion criteria? • What is the quality of information?(e.g. data entry) • How complete is the coverage? • What kind of information is coded? for Routine collected statistics and administrative data you must take into account that : 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.	• HTA Core Model For Screening Technologies (2014) • AHRQ User's guide - Registries for evaluating patient's outcomes (Gliklich et al .2010)	

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490 **3.9 Data synthesis**

Standard procedure	References	Done
Define a clear plan to • construct a descriptive summary of the included studies *N.B.: you can do it by tabulating details about study type, interventions, numbers of participants, a summary of participant characteristics, outcomes, method to collect adverse events. An indication of study quality or risk of bias may also be given in this or a separate table. Data synthesis should include text and tables to provide an initial descriptive summary and explanation of the characteristics and findings of the included studies.* • decide whether and how to perform a narrative synthesis and or a quantitative synthesis of results of studies (table / forest plot / range of estimates / meta-analysis). *N.B.: a narrative synthesis of studies may be undertaken where studies are too heterogeneous (either clinically or methodologically) to combine in a meta-analysis, but even where a meta-analysis is possible, aspects of narrative synthesis will usually be required in order to fully interpret the collected evidence.* • Summarize characteristics of single included studies according to recommendations from the Model for Rapid REA of pharmaceuticals Data Synthesis • Develop a preliminary synthesis of findings of included studies • Report results by each study design / source of data • Summarize in a table the results by group of included studies/data according to recommendations from the Model for Rapid REA of pharmaceuticals • Summarize in a table the results by group of included studies/data according to recommendations from the Model for Rapid REA of pharmaceuticals • Describe the safety profile of the technology versus the comparator(s),	• Chapter 2, Systematic reviews of clinical tests, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • Chapter 4, Systematic reviews of adverse effects, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • Safety domain, HTA Core Model ver 1.5 April 2014 • Chapter 2.7, Methods: Interpreting evidence, in Model for Rapid REA of pharmaceuticals (2013) • Appendix 5, Recommendations of guidelines on methodological issues, Safety, in Model for Rapid REA of pharmaceuticals 2013.	Yes No (explain)

with special regard to the most frequent, serious and severe adverse reactions. • A table is preferable for the comparison of the safety profile of the new pharmaceutical and the comparator(s). • Variation in results across studies should be investigated and explore relationships within and between studies • Quantitative results should be expressed as point estimates together with associated confidence intervals and exact p-values. *N.B.: simply describing the studies is not sufficient for a synthesis. The defining characteristic of narrative synthesis is the adoption of a textual approach that provides an analysis of the relationships within and between studies and an overall assessment of the robustness of the evidence.*		

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492 **3.10 Grading of quality of evidence**

Standard procedure	References	Done
If appropriate and possible, assess and report quality of evidence (grading): - for single studies - for single important outcomes/adverse events across studies *N.B.: for this procedure you must take into account that* *1) for overall rating of the quality of evidence for each outcome you could apply the GRADE method* *2) for overall rating of the quality of evidence according to the GRADE method you have to prepare Summary of Findings tables. In this case the GRADE method considers – in addition to risk of bias/limitations - also publication bias, imprecision of results, inconsistency of results, indirectness of results*	• GRADE method - Guyatt et al. 2011a - Balshem et al. 2011 - Guyatt et al. 2011b - Guyatt et al. 2011c - Guyatt et al. 2011d - Guyatt et al. 2011e - Guyatt et al. 2011f - Guyatt et al. 2011g - Guyatt et al. 2013 - Schunemann et al. 2008	Yes No (explain)

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494 **3.11 Reporting**

Standard procedure	References	Done

Define important terms in a glossary Reporting is performed in three phases: the result cards, the domain reports and the full report In the result cards the authors report the detailed methods and results for each research question separately. The cards are compiled in a domain report amended with chapters for domain specific methods, summary of main results, and discussion. Finally, all domain reports are taken together, and amended with the benefit-harm analysis and overall summary and discussion. Enter the results according to the instructions from the HTA Core Model Online 2012. Chapter 2.2.4 Phase 4: Entering the results	• Chapter 2.8, Methods: Reporting, in Model for Rapid REA of pharmaceuticals (2013) • Chapter 2.2.4, Phase 4: Entering the results, in HTA Core Model Online (2014)	Yes No (explain)

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2.8 Domain specific issues: Effectiveness of the technology (EFF)

Aim

The aim of this guidance is to describe the necessary information and practical procedures/steps for the production of the information (result cards) corresponding to Assessment Elements for the Core HTA's Effectiveness domain.

Evidence base

The following conceptual framework was applied: first, methodological deliverables by EUnetHTA were included and consulted to design the structure for a systematic review of effectiveness. Then, handbooks or manuals for producing systematic reviews from institutions contributing to the methodology of systematic reviews were non-systematically consulted from specific websites and included. Finally, tools and methods for single specific procedural steps were non-systematically searched and included. The documents included were compared for consistency.

The following documents were used in order to define the general design for the practical guidance of procedures:

- Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011);
- CRD's Guidance for Undertaking Reviews in Healthcare (Centre for Reviews and Dissemination 2009).
- HTA Core Model Handbook (2014);
- EUnetHTA Model for Rapid REA of pharmaceuticals (2013);
- PRISMA Statement (Moher et al. 2009);
- In addition to the above documents, the followings were used to define single procedural steps:
- AMSTAR instrument (Shea et al. 2007);
- Bossuyt et al. (2006);
- Cochrane Handbook for DTA Reviews (Diagnostic Test Accuracy Working Group 2011);
- EUnetHTA Assessment Element for Diagnostic Technologies (2014)
- EUnetHTA Assessment Element for Screening Technologies (2014)
- EUnetHTA Assessment Element for Medical and Surgical Interventions (2014)
- EUnetHTA Methodological guidelines for rapid relative effectiveness assessment (REA) of Pharmaceuticals developed in WP5 (2013)
- HTA Core Model on Abdominal Aorta Aneurysm Screening (Jefferson et al. 2013a)
- HTA Core Model on Prognostic tests for breast cancer recurrence (uPA/PAI-1 [FEMTELLE], MammaPrint, Oncotype DX) (Jefferson et al. 2013b)
- GRADE method (Balshem et al. 2011, Guyatt et al. 2011a, Guyatt et al. 2011b, Guyatt et al. 2011c, Guyatt et al. 2011d, Guyatt et al. 2011e, Guyatt et al. 2011f, Guyatt et al. 2011g, Guyatt et al. 2013, Schünemann et al. 2008);
- Methods guides on medical test reviews (AHRQ 2012).
- Newcastle-Ottawa Scale (Wells et al. 2008);
- QUADAS 2 tool (Whiting et al. 2011);
- QUIPS tool (Hayden et al. 2013)
- STARD Checklist (Bossuyt et al. 2003);

The guidance is structured as a table containing:

1. a first column with an assertive sentence for the action requested, labelled as "*Standard procedure*". If needed, details, suggestions and description of the most common pitfalls are provided.
2. a second column, labelled as "*References*", specifying the reference(s) at the basis of the action, where more details for accomplishing the procedure can be found.

3. a third column, labelled as "*Done*", to check if each action is done or not and why.

If different approaches and methodologies are needed, every procedural step is distinguished for each of the following types of technology: (1) Medical and Surgical Interventions, (2) Diagnostic Technologies, (3) Screening Technologies, (4) Prognostic technologies. Unless otherwise specified, the procedural step is to be considered applicable for all four types of technology.

Practical guidance

In this chapter the procedural steps needed to produce the result cards corresponding to Assessment Elements for the Effectiveness domain are reported.

To complete the Assessment Elements for the Effectiveness domain one or more Systematic Reviews, answering each selected issue, need to be carried out. There are pre-defined steps in producing a systematic review (CRD's Guidance for Undertaking Reviews in Healthcare 2009, Higgins et al. 2011, HTA Core Model Handbook 2012, HTA Model for Rapid REA of pharmaceuticals 2013, Moher et al. 2009):

3.1. Selection of the topics and issues from the HTA Core Model Assessment Elements
3.2. Definition of research questions
3.3.Definition of inclusion criteria for considering studies
3.4.Systematic search of evidence
3.5.Selection of the studies
3.6.Data extraction
3.7.Methodological quality assessment
3.8.Data synthesis
3.9. Grading of quality of evidence
3.10.Reporting

3.1 Selection of the topics and issues from the HTA Core Model Assessment Elements

Standard procedure	References	Done
Select the topics and issues from the HTA Core Model Assessment Elements *N.B.: Methods specific to conduct a systematic review of a prognostic test are not well established. Currently there are only three applications of the HTA Core Model: medical and surgical interventions, diagnostic technologies, and screening technologies. While awaiting for specific methodological guidance on prognostic technologies, refer to guidance for diagnostic technologies. However, there are fundamental differences in the assessment of diagnostic and prognostic tests, thus consider that HTA Core assessment element questions for diagnostic technologies are thus not suited for prognostic*	• Chapter 2.2.2 Phase 2: Protocol design, in HTA Core Model Handbook (2014) • Assessment Element for Diagnostic Technologies (2014) • Assessment Element for Screening Technologies (2014) • Assessment Element for Medical and Surgical Interventions (2014) • Clinical Effectiveness, Methodology Description Chapter, in HTA core model on Prognostic tests for breast cancer recurrence (Jefferson et al. 2013b)	Yes No (explain)

technologies.	• Chapter 12. Systematic Review of Prognostic Tests, in Methods Guide for Medical Test Reviews (AHRQ 2012)	

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658 **3.2 Definition of research questions**

Standard procedure	References	Done
Define research question(s) according to the PICOD system PICOD stands for participants, interventions, comparisons, outcomes, and study design.	• Chapter 2.2.2, Phase 2: Protocol design, in HTA Core Model Handbook (2014) • Appendix 3, Systematic review of the literature, in Model for Rapid REA of pharmaceuticals 2013. • PRISMA Statement (Moher et al. 2009)	Yes No (explain)
Outcomes relevant to the technology should be listed and differentiated in Primary, Secondary and Surrogate	• Chapter 5, Defining the review question and developing criteria for including studies, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011) • Chapter 2, Methods, in Model for Rapid REA of pharmaceuticals (2013)	Yes No (explain)

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660 **3.3 Definition of inclusion criteria for considering studies**

Standard procedure	References	Done
Define "Criteria for considering studies for inclusion" according to elements of PICOD.	• Chapter 5, Defining the review question and developing criteria for including studies, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011)	Yes No (explain)
Relevant to all " Topics" from Assessment Elements (i.e. all outcomes, including harms and adverse effects) of Medical and Surgical Interventions: the inclusion criteria must be established for the following elements: - Population/patient characteristics - Types of interventions - Types of comparators - Relevant outcomes - Study design - Publication type	• Chapter 2, Systematic reviews of clinical tests, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • Chapter 5, Defining the review question and developing criteria for including studies, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011) • Chapter 2, Methods, in Model	Yes No (explain)

- Publication date - Language *N.B.: for this procedure you must take into account that* *3) If systematic reviews or HTA reports are available you should value if they could be adapted or updated* *4) The best evidence is based on RCTs and SR(s) of RCTs, so you have to consider inclusion/exclusion criteria for both study designs.* 5) *If you anticipate few RCTs, you should consider whether to include non RCTs studies and which types of non RCTs studies* 6) *If cohort studies or case series are included, specify if studies with a retrospective design are suitable for inclusion* 7) *If case series are included, define a minimum number of study's participants as inclusion criterion* 8) *Ideally all relevant studies should be included but if this is not feasible they should be identified and you should specify the reason for exclusion recorded* 9) *Depending on the novelty of the technology you should value if you include only studies published in peer-review studies or if you will also take into account information from conference abstracts, unpublished data.* 10) *You should value if you include all studies or only those published in the last years* 11) *Inclusion/Exclusion criteria should be clearly presented in the report*	for Rapid REA of pharmaceuticals (2013) • Effectiveness Chapter. HTA Core Model for Medical and Surgical Interventions (2.0)	
Relevant to all " topics" from Assessment Elements (i.e. all outcomes including harms and adverse effects) of Diagnostic Technologies, Screening Technologies and Prognostic Technologies the inclusion criteria should clearly define the following elements - population/patient characteristics (health care setting, stage of the disease, severity, age, etc) - types of index tests *N.B.: For some tests you must take into account that there will be studies analysing only the index test without considering the comparator test. In this case you have to specify whether studies without*	• Chapter 6, Developing criteria for including studies, in Cochrane Handbook for DTA Reviews (Diagnostic Test Accuracy Working Group 2011) • Chapter 2, Systematic reviews of clinical tests, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • STARD Checklist (Bossuyt et al. 2003) • Bossuyt et al. (2006) • EUnetHTA GL Meta-analysis of diagnostic test accuracy studies (in development)	Yes No (explain)

head-to-head comparisons are to be included or excluded. - types of comparator tests *N.B: If data on comparator are not available from head to head comparison, you will have to decide whether to include indirect evidence.* - types of target conditions *N.B.: The authors should define clearly the target condition/s that will be considered (i.e. diagnosis of specific condition, disease stage, treatment response, etc.)* - reference standards - types of outcome (diagnostic accuracy and clinical outcomes) - types of studies *N.B.: for this procedure you must take into account that* *1) the best evidence for diagnostic accuracy is based on diagnostic test accuracy studies and SR(s) of diagnostic test accuracy studies, so you have to consider inclusion/exclusion criteria for both study designs.* *2) it could be important - for the transferability and interpretation of results – to establish "a priori" the role of test and its position in the diagnostic pathway according to the following labels: Triage, Replacement, Add-on* 3) *issues of intra and inter-observer reliability of the tests refer to the Description and technical characteristics of technology.*		

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662 **3.4 Systematic search of evidence**

Standard procedure	References	Done
Conduct a comprehensive systematic search of evidence for each research question searching: - General medical databases - Topic specific databases - Systematic review databases/HTA databases - Trial registers - Grey literature through hand searching if appropriate - Unpublished studies (seek additional information from manufacturers, and EMA clinical study report request procedure or agencies?)	• Appendix 3, Systematic review of the literature, in Model for Rapid REA of pharmaceuticals (2013) • Chapter 6, Searching for studies, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011) • Chapter 7, Searching for studies, in Cochrane Handbook for DTA Reviews (Diagnostic Test Accuracy Working Group	Yes No (explain)

For each search draft a sufficiently detailed report of searches and databases should be provided to allow search to be reproduced. The search process should be explicitly defined including search strategy. A flow chart with number of studies retrieved, studies included and excluded and reasons for exclusion is recommended. You should update the search at the end of the review	2011) • Agency for Healthcare Research and Quality. Methods guide for effectiveness and comparative effectiveness reviews http://www.effectivehealthcare.ahrq.gov/ehc/products/60/318/CER-Methods-Guide-140109.pdf PDF pp.103, 125, 136-8, 166. January 2014. • **EUnetHTA GL Process of information retrieval (in development)**	Yes No (explain)
Use bibliographic software to manage references.		Yes No (explain)

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664 **3.5 Selection of the studies**

Standard procedure	References	Done
Perform the selection of studies through the following steps: - selection of potentially relevant titles and /or abstracts and retrieval of full-texts - assessment of full papers considered as potentially relevant - inclusion of the final set of studies *N.B.: for this procedure you must take into account that* *2) Assessment of eligibility of studies, and extraction of data from study reports, should be done by at least two people, independently* *Studies, rather than publications, are the unit of interest of the review, therefore multiple publications of the same study need to be linked together. Duplicated studies should be eliminated.*	• Appendix 3, Systematic review of the literature, in Model for Rapid REA of pharmaceuticals (2013) • Chapter 7, Selecting studies and collecting data, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011) • Chapter 1, Core principles and methods for conducting a systematic review of health interventions, in CRD's Guidance for Undertaking Reviews in Healthcare (2009)	Yes No (explain)

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666 **3.6 Data extraction**

Standard procedure	References	Done
Define all data you have to collect and design a standardized data collection form	• Template 5, Table for reporting results from clinical trials, in Model for Rapid REA of pharmaceuticals (2013) • Chapter 7, Selecting studies	Yes No (explain)

Describe how the data extraction process is to be performed in terms of - the data categories and information requirements that are to be collected - how verification of extracted data from each report will be verified (e.g. extraction by two review authors, independently) - piloting, training and existence of coding instructions for the data collection form; - how data are extracted from multiple reports of the same study - how disagreements are handled if more than one author extracts data from each report *N.B.: for this procedure you must take into account that* *1) When you design the data extraction form you should take into account the aim of the report, research questions but also the information that will be relevant for quality assessment and analysis of results* *2) if appropriate, you need to consider separately how to manage data from primary studies and data from SRs* *3) for diagnostic accuracy studies you should consider also specific data to be extracted (i.e. raw data to calculate pre-test probability/prevalence of disease, raw number of true and false positive, true and false negative, ecc.)*	and collecting data, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011) • Chapter 1, Core principles and methods for conducting a systematic review of health intervention, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • Chapter 2, Systematic reviews of clinical tests, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • EUnetHTA GL Meta-analysis of diagnostic test accuracy studies (2014)	Yes No (explain)

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668 **3.7 Methodological quality assessment**

Standard procedure	References	Done
Use validated frameworks and tools for the methodological quality/risk of bias/internal validity assessment of included studies *N.B.: for this procedure you must take into account that* *4) you must apply different tools for different study scope and design (i.e. primary studies vs SRs, effectiveness studies vs diagnostic accuracy studies, RCTs vs non-RCTs)* *5) you must take into account that simply grading studies is not sufficient and that you should also assess the appropriateness of the study to resolve the research question* *6) you should refer to risk of bias specific for*	• Guideline 8, Levels of evidence: Internal validity (of randomized controlled trials, in Model for Rapid REA of pharmaceuticals (2013) • Guideline 9, Levels of evidence: Applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals, in Model for Rapid REA of pharmaceuticals (2013) • Chapter 8, Assessing risk of bias in included studies, in Cochrane Handbook for Systematic Reviews of	Yes No (explain)

each type of technology (MST, DT, ST) and purpose (effectiveness, diagnostic accuracy) *7) when you include a SR you should distinguish the quality of the SR itself from the quality of results obtained from the primary studies included into the SRs*	Interventions (Higgins et al. 2011) • Chapter 13, Including non-randomized studies, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011) • Chapter 9, Assessing Methodological Quality, in Cochrane Handbook for DTA Reviews (Diagnostic Test Accuracy Working Group 2011) • Chapter 1, Core principles and methods for conducting a systematic review of health interventions, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • Chapter 2, Systematic reviews of clinical tests, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • EUnetHTA GL Meta-analysis of diagnostic test accuracy studies (2014)	
To assess methodological quality/risk of bias/internal validity of systematic reviews you could refer to the AMSTAR instrument or to the NOKC checklist for systematic reviews	• Shea et al. 2007 • Appendix EFF-1 Section 4, in Abdominal Aorta Aneurysm Screening (Jefferson et al. 2013a)	Yes No (explain)
To assess methodological quality/risk of bias/internal validity of RCTs refer to the risk of bias system proposed by the Cochrane Handbook for Systematic Reviews of Interventions	• Chapter 8, Assessing risk of bias in included studies, in Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011)	Yes No (explain)
To assess methodological quality/risk of bias/internal validity of cohort studies refer to the Cochrane Acrobat-NRSI tool. www.riskofbias.	• Cochrane Handbook for Systematic Reviews of Interventions 2011. Chapter 13: Including non-randomized studies • Wells et al.	Yes No (explain)
To assess methodological quality/risk of bias/internal validity of diagnostic accuracy studies refer to the QUADAS 2 tool	• Chapter 9, Assessing Methodological Quality, in Cochrane Handbook for DTA Reviews (Diagnostic Test Accuracy Working Group 2011) • Whiting et al. (2011)	Yes No (explain)
To assess methodological quality/risk of bias/internal validity of prognostic studies you could	• Hayden et al. (2013)	Yes No

refer to the QUIPS tool		(explain)

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670 **3.8 Data synthesis**

Standard procedure	References	Done
Define a clear plan to • construct a descriptive summary of the included studies *N.B.: you can do it by tabulating details about study type, interventions, numbers of participants, a summary of participant characteristics, outcomes and outcome measures. An indication of study quality or risk of bias may also be given in this or a separate table. Data synthesis should include text and tables to provide an initial descriptive summary and explanation of the characteristics and findings of the included studies.* • decide whether and how to perform a narrative synthesis and or a quantitative synthesis of results of studies (table / forest plot / range of estimates / meta-analysis). *N.B.: a narrative synthesis of studies may be undertaken where studies are too heterogeneous (either clinically or methodologically) to combine in a meta-analysis, but even where a meta-analysis is possible, aspects of narrative synthesis will usually be required in order to fully interpret the collected evidence.* Data Synthesis • Develop a preliminary synthesis of findings of included studies • Report results by each outcome • Quantitative results should be expressed as point estimates together with associated confidence intervals and exact p-values. • Variation in results across studies should be investigated • Explore relationships within and between studies • Propose an interpretation of how the intervention works, why and for whom *N.B.: simply describing the studies is not sufficient for a synthesis. The defining characteristic of narrative synthesis is the adoption of a textual approach that provides an analysis of the relationships within and between studies and an overall assessment of the robustness of the evidence.*	• Chapter 1, Core principles and methods for conducting a systematic review of health interventions, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • Chapter 2, Systematic reviews of clinical tests, in CRD's Guidance for Undertaking Reviews in Healthcare (2009) • Chapter 2.7, Methods: Interpreting evidence, in Model for Rapid REA of pharmaceuticals (2013) • EUnetHTA GL Meta-analysis of diagnostic test accuracy studies (2014)	Yes No (explain)

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672 **3.9 Grading of quality of evidence**

Standard procedure	References	Done
If appropriate and possible, assess and report quality of evidence (grading): - for single studies - for single important outcomes across studies *N.B.: for this procedure you must take into account that* *3) for overall rating of the quality of evidence for each outcome you could apply the GRADE method* *4) for overall rating of the quality of evidence according to the GRADE method you have to prepare Summary of Findings tables. In this case you should consider – in addition to risk of bias/limitations - also publication bias, imprecision of results, inconsistency of results, indirectness of results* *5) for Diagnostic Technologies and Prognostic Technologies studies publication bias, imprecision of results, inconsistency of results have not consolidated methods to be assessed with*	• GRADE method - Guyatt et al. 2011a - Balshem et al. 2011 - Guyatt et al. 2011b - Guyatt et al. 2011c - Guyatt et al. 2011d - Guyatt et al. 2011e - Guyatt et al. 2011f - Guyatt et al. 2011g - Guyatt et al. 2013 • EUnetHTA GL Meta-analysis of diagnostic test accuracy studies (2014)	Yes No (explain)

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674 **3.10 Reporting**

Standard procedure	References	Done
Check relations to other domains (SAF) to avoid double work Define important terms in a glossary Reporting is performed in three phases: the result cards, the domain reports and the full report In the result cards the authors report the detailed methods and results for each research question separately. The cards are compiled in a domain report amended with chapters for domain specific methods, summary of main results, and discussion. Finally, all domain reports are taken together, and amended with the benefit-harm analysis and overall summary and discussion. • Enter the results according to the instructions from the HTA Core Model Online 2014. Chapter 2.2.4 Phase 4: Entering the results	• Chapter 2.8, Methods: Reporting, in Model for Rapid REA of pharmaceuticals (2013) • Chapter 2.2.4, Phase 4: Entering the results, in HTA Core Model Online (2014)	Yes No (explain)

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2.9 Domain specific issues: Costs, economic evaluation of the technology (ECO)

Aim

The aim of this guidance for the ECO domain is to provide HTA Core Model domain team members with practical guidance on a list of issues which have to be taken into account when developing the domain content.

Evidence base

The contents of this chapter were developed on the basis of methodological deliverables by EUnetHTA, as well as from practical experience from previous core HTA projects within EUnetHTA Project (2006-2008) and EUnetHTA Joint Action 1 (2010-2012) and during the development of the 1st Core HTA in the framework of EUnetHTA JA2 WP4 activities. The following documents have been consulted:

- HTA Core Model for Medical and Surgical Interventions (2.0)
- HTA Core Model for Diagnostic Technologies (2.0)
- HTA Core Model for Screening Technologies (2.0)
- HTA Core Model Handbook v.1.5.
- EUnetHTA WP5 JA2, Relative effectiveness of pharmaceuticals, Procedure manual for piloting REAs, V3
- EUnetHTA WP5 JA2, Rapid assessments of other health technologies, Procedure manual for piloting rapid assessments, V3
- EUnetHTA core HTA on Abdominal Aorta Aneurysm Screening (Jefferson et al. 2013a)
- EUnetHTA core HTA on Prognostic tests for breast cancer recurrence (uPA/PAI-1 [FEMTELLE], MammaPrint, Oncotype DX) (Jefferson et al. 2013b)

Practical guidance

Readers shoud consult [EUnetHTA Guideline on Economic evaluations: SAG / Public consultation finalised (DEC 2014), work on 212 received comments and preparation of final version to be published in MAR 2015]

Preparing for the writing phase

The roles of authors/co-authors/reviewers as well as suggested ways of the division of tasks are discussed in the current document (Chapter: *1.5 Project management and forming teams*). Domain team members could consider familiarizing themselves with the relevant HTA Core Model (pharmaceuticals, diagnostics, surgical procedures etc.) already developed by EUnetHTA and available on the EUnetHTA website as well as the guidance on handling the electronic environment (Chapter: *General issues: handling the electronic environment* in the current document). Relevant documents include:

- HTA Core Model for Medical and Surgical Interventions (2.0)
- HTA Core Model for Diagnostic Technologies (2.0)
- HTA Core Model for Screening Technologies (2.0)
- HTA Core Model Handbook V 1.5

Domain team members complete the Conflicts of Interest Declaration Form (COI Form, Appendix 4) prepared by EUnetHTA and submit it to the WP LP, so that potential problems will be addressed.

Scoping phase

The primary investigator (PI) collaborates with other Domains' PIs for the development of the PICO questions so that economic evaluation papers are identified during the centralized initial literature search.

The operational steps for developing the content for the "COSTS, ECONOMIC EVALUATION OF THE TECHNOLOGY" domain are:

1. Selection of the most relevant topics from the relevant HTA Core Model
2. Search for information in the data sources
3. Assessment of the quality of the information
4. Analysing and synthesis
5. Reporting of results

1. Selection of the most relevant topics from the relevant HTA Core Model

Selection of Assessment elements of the respective HTA Core Model applications. which are also research questions relevant to the scope of the project. **Search for information in the data sources**

Topic issues included in the ECO domain are:

- Resource utilization (identification, measurement, valuation of resources)
- Measurement and estimation of outcome(s)
- Examination of costs and outcomes
- Characterising uncertainty
- Characterising heterogeneity
- Validity of the model(s)

At this point, investigators will have access to text already developed by the CUR, TEC, SAF, EFF, ORG domains . Relations with other domains need to be taken into consideration. At this stage, domain team members can discuss the approach to be adopted i.e. whether the domain will provide a review of existing economic evidence or an economic model will be developed and populated or both. This would facilitate information gathering, as information sources vary depending on the approach. Justification of the approach adopted should be provided.

Data to be used in the ECO domain may be located as part of the *overall search* conducted for the whole project during the scoping phase. However, it is highly likely that additional literature searches will be necessary.

In addition to the guidance included in the guideline "Methods for health economic evaluations – A guideline based on current practices in Europe", to be published in April 2015, a collection of literature that provides a solid scientific basis covering all the methodological aspects of economic evaluation is provided under Bibliography.

Reporting of results

It is suggested that authors work on domain result templates that can be downloaded from the Online HTA Model Tool (Research Tab of the respective project). Domain result templates include the research questions in the domain. On the same tab, a reference manager guide and the EUnetHTA citation style for Endnote are available, as well as a draft template of a study card (its use is optional). Authors work mostly on text documents. Changes they make on the text should be marked either by using the Track Changes

tool in Word or by using different font colors. Authors can also decide on who will be responsible for accepting/rejecting changes and finalizing the text.

In the reporting, use of summary tables, graphs, schematic patient flows, model representations is encouraged as they facilitate communication and understanding of findings.

Internal Review

It is recommended that *internal reviewers (IR)* are given enough time to familiarize themselves with the domain text, as previous experience has shown. It was also suggested that IRs have access to the whole Core HTA draft text and not just the domain text.

IRs should provide their comments through a comments table.

PIs and Is reply to the comments by *IRs* using the "Authors Reply Form on Stakeholders Consultations" document. Template is available in the Appendix 5.

Comments by SAG

PIs and Investigators reply to the comments by SAG using the "Authors Reply Form on Stakeholders Consultations" document. Template is available in the Appendix 5.

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- Methods for health economic evaluations – A guideline based on current practices in Europe", to be published in April 2015

2.10 Ethical aspects of the technology (ETH)

Aim

To provide HTA Core Model users with a synthetic list of specific issues, tools, and methods to be taken into account to carry out the ethical analysis in the Core HTA process.

Evidence base

Methodological deliverables by *European Network for Health Technology Assessment (EUnetHTA) HTA Core Model* (2014) for Medical and Surgical Interventions (1.0R, 1.1, 2.0), for Diagnostic Technologies (1.0R, 1.1, 2.0), for Screening Technologies (1.0, 2.0), for Pharmaceuticals (2.0) were consulted and used in this chapter to collect all available evidence to design the structure for a systematic analysis on ethical aspects of a certain health technology. Current literature on methodological aspects related to HTA Ethical domain was considered.

Practical guidance

The operational steps for assessing ethical aspects of a health technology are:

- Defining the focus of the overall assessment
- Collecting ethically relevant information and assessing the quality of the information;
- Processing of available literature and extraction of ethically relevant aspects;
- Producing the core of ethical analysis;
- Methods for addressing HTA ethical analysis;
- Synthesizing, reporting and interpreting the ethical analysis and evidence;
- Transferability of ethical analysis;
- Overlap with other domains (e.g. legal and social)

Defining the focus of the overall health technology assessment

The entire HTA working group defines the focus within the topic, the specific questions to be answered, the study inclusion criteria, the primary outcome points for the analysis of the consequences of implementing/not implementing/disinvesting an health technology (e. g.: efficacy, safety, effectiveness, cost implications). These choices are “value-laden” and they need to be considered carefully before proceeding to literature review as they can have a major impact on the content and conclusions of the assessment.

Collecting ethically relevant information and assessing the quality of the information

The ethical domain information sources for its specific analysis are the following:

- *Ethics literature* linked to the object of the analysis, from (general and HTA dedicated) bibliographic sources. If these are not available, literature on issues analogous to the matter under discussion should be considered;
- *Ethically relevant documentation from factual databases* that provide information in the form of guidelines for diagnosis and treatment, patient indications/contraindications, and other authoritative information, like professional standards/guidelines/reports, Codes of ethics by Colleges of healthcare professionals, statements of Scientific Societies, industry and government monographs, regulatory documents, market research reports, policy and research institute studies, publications of special panels and commissions, conference proceedings (e.g.: World Medical Association; Italian College of Physicians) and HTA reports from national, federal, regional bodies (e.g.: INAHTA, European Network for Health technology Assessment (EUnetHTA); UK National Institute for Clinical Excellence (NICE); Canadian Agency for Drugs and Technologies in Health (CADTH), etc.).
- Results produced by other domains involved should be analyzed for their possible ethical relevance, especially in the case of very scarce or lacking specific ethics literature.
- *Stakeholder opinion (e.g.: experts, public, patients, service users, industry, organizational and healthcare professionals, etc.) through meetings/hearings or by primary studies*, might consent to get information/inputs – to be analysed from the qualitative point of view – on aspects that could not be identified by the content or methodological expert group or from the literature review. Experts' opinions are considered the lowest level of evidence.
- *Discussions within the HTA working group*. Debate among researchers involved in the assessment process is an effective resource in identifying ethical aspects related to the technology in discussion.

No baseline quality criteria are of available in literature on the assessment of the ethical impact of the technology in question, but a possible checklist could be:

a. the inclusion of the publications in peer-reviewed journals in international databases (e.g.: PubMed, Embase, etc);
b. the inclusion of the retrieved general and specific documentation/literature in recognized highly qualified institutional bodies: for "general" documentation an example could be professional standards/guidelines, Codes of ethics by Colleges of healthcare professionals/Scientific Societies; while for "specific" documentation, among others: INAHTA, NICE; CADTH. Although this literature can be timely and cover aspects of technologies that are not addressed in mainstream sources, it is usually not subject to peer review, and must be scrutinized accordingly.

- For literature from other HTA domains of possible ethical interest, the current standard quality criteria adopted for different domains are assumed (e.g.: GRADE and PICO methodologies for EFF domain).

Processing of available literature and extraction of ethically relevant aspects

The first task of an ethical analysis in an HTA process is the *processing of literature*. In fact, as the *HTA Core Model* suggests literature search focused only on the technology in question may seldom give access to articles relevant to the ethical evaluation. A natural starting point could be:

- to include keywords related to ethics to the literature search needed to cover the other areas of the HTA process;
- to hand-search published HTA reports (ethical considerations are often integrated in the reports), and perform an Internet search for reports, proceedings and books, etc;
- to perform a systematic literature review that will cover all the ethical and moral issues identified during the process is challenging. Ethically relevant issues are identified during the entire HTA process, and the literature searches thus commonly repeated when new ethically relevant issues are identified. The extended literature search should not be focused only on the technology in question, but cover other related technologies with similar ethical challenges. The detailed literature search should include all relevant sources on ethical aspects of the technology in question. A suggestion for databases and potentially useful MeSH terms was identified by Droste (cf. Droste et al 2003, 2010);
- Finally, ethical analysis in HTA needs to consult a wider range of sources of literature than would normally be considered for scientific evidence on clinical effectiveness.

Producing the core of ethical analysis in an HTA process

An ethicist should be *responsible for drafting, facilitating and reporting the ethical analysis*. Preferably, ethical considerations should be introduced as early as possible in the HTA process. The responsible person for the ethical analysis should ensure that the moral issues are considered by the whole group during the entire process.

A successful ethical analysis should always be carried out together with the content experts and not seen as an add-on that can be conducted by separate ethicists alone. Ethical analysis is an ongoing process that lasts throughout the HTA project. Ethical and moral issues should be considered early on while analyzing other aspects of the technology and, vice versa, the ethical analysis is dependent on the results and insights gathered for the other domains. However, if the only alternative is to do an “add-on” ethical analysis this is most likely better than no ethical analysis at all.

Considerations on ethical aspects relate to two areas: 1. questions related to the HTA process (selection of topic, outcomes, methods, evaluating the importance of ethical analysis and planning it); 2. questions related to implementing/not implementing or disinvesting the technology in an health care service.

Methods for addressing HTA ethical analysis

The choice of methods to perform an ethical analysis in an HTA process depends on a number of interacting factors: a. the type of technology being assessed; b. the role and authority of the HTA organization in the national decision-making procedure; c. the time and resources available for the assessment; d. the methodological expertise and experience with ethical analysis that are available within the organization; e. the socio-cultural context.

There are many possible approaches, ranging from deontological to teleological perspectives (casuistry; coherence analysis; interactive, participatory HTA approach; principlism; social shaping of technology; wide reflective equilibrium, the “triangular model” based on the human person - centred approach; axiological (Socratic) approach). The debate about them highlighted that each approach has strengths and weaknesses in HTA context; consequently, no single approach is probably sufficient when it is applied alone. Moreover, since the moral issues of a technology are closely linked to the context of its development, uptake, and use, approaches for HTA ethical domain should be context-sensitive. (Burls et al, 2011).

After a clear declaration of the approached assumed to conduct the ethical analysis, it is useful to set up a list of possible research questions to systematize the fundamental issues of ethical interests

(beneficence/non maleficence, autonomy, respect for persons, justice and equity, ethical relevance of legislation, ethical consequences of the HTA). *HTA Core Model Assessment Elements List* is a useful tool for this purpose (EUnetHTA, 2014).

Some issues deal with direct consequences of the implementation/not implementation/disinvesting (simple facts, e.g. can the technology harm the patient). Many issues deal with questions that need careful consideration that will provide a thorough overview of the value-laden aspects that need to be taken into account when deciding on implementation (e.g. balance between benefit and harm). A minority of issues cover areas that lead to clear conclusions (e.g. whether legislation is fair and adequate).

Synthesizing, reporting and interpreting the ethical analysis and evidence

Once ethical values at stake or in conflict for the health technology in question have been identified and analyzed through a particular ethical approach and methodology, the results have to be synthesized and reported transparently so that they can be considered when deciding whether to implement/not implement/disinvest a technology.

No single solution to every ethical problem exists, nor is it possible to list ethical issues according to a commonly agreed weighted value. Answers to the core set of issues may also reflect the wide variety in personal morals and values within the society. The synthesis of ethical analysis has to be performed in an open way. Either the interests of various stakeholders are kept as "unweighted" as possible, or the weighing is done transparently i.e. describing the procedure and participants of the analysis.

Ideally, the decision on "whose values are to be weighted" need to be in the hands of the decision makers. There can be different decision makers for different types of technologies within the same country and between countries. The ideal way to present the synthesis of the analysis may vary accordingly.

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

The results of the ethical analysis will usually be reported as a separate chapter within the HTA report, to guarantee 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 decision to implement/not implement/disinvest a new technology requires careful decision on the balance between benefit and harm, cost-effectiveness, reallocation of resources, etc. Discussing the context-specific moral issues within the respective chapter (e.g.: effectiveness, safety, and costs) may thus also help the decision makers to identify various scenarios and find the best for the common good.

Transferability of ethical analysis

The ethical analysis and its outcome have to be described so that their transferability across different national or local settings could be evaluated.

Many of the ethical implications are common to various nations, but some value-laden issues are likely to be *country-* or *community –specific*, and will crucially relate to factors such as the ‘social

contract', the country's healthcare financing system and the country's economic growth prospects, relying on local values, stakeholder attitudes and available health care resources.

Overlap with HTA legal and social domains

Ethical analysis cannot be "separated" from the assessment of legal and social aspects related to a particular health technology. Sometimes, these domains overlap with the ethical analysis, though the angle of evaluation may differ (e.g.: the legal framework forms one of the fundaments for professional ethics).

The societal consequences of implementing/not implementing/disinvesting an health technology may differ 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/not implementation/disinvestment of an health technology will not only have an effect on health, functional abilities and psychosocial well-being, but also on social networks and need of support.

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2.11 Domain specific issues: Organisational aspects of the technology (ORG)

Aim

This chapter provides guidance for assessing the organizational impact of new technologies.

Evidence base

The following documents were consulted to collect all available evidence at the basis of the guidance:

- HTA Core Model Handbook (2014);
- HTA Core Model For Screening Technologies (2014)
- EUnetHTA Assessment Element for Screening Technologies (2014)
- EUnetHTA Assessment Element for Diagnostic Technologies (2014)
- EUnetHTA Assessment Element for Medical and Surgical Interventions (2014)

Practical guidance

The organizational domain of a healthcare process represents one of the most complex aspects of the work. This is because the relationship between many variables acting in an organizational context and the final results are not foreseeable.

The search for evidence for the evaluation of the organizational impact of a technology can follow two methods: an evidence-based literature analysis and a specific collection of data (quantitative and qualitative evidence).

The relevant operational steps are:

1. to select the most relevant topics from one of the HTA Core Models
2. (Diagnostic Technologies (2008), Screening Technologies and Medical and Surgical Interventions) and search for information in the data sources
3. to data extract
4. to assess the quality of the information gained
5. to produce analysis and synthesis
6. to report the results

1. Selection of the most relevant topics/issue and search of information

The organizational domain is based on four possible topics: “process”, “structure”, “management” and “culture”.

The first step consists of the selection of the topics and issues from the HTA Core Model Assessment.

Describe the information about the “process”:

- Process description
- Personnel, training and resources
- Interaction and communication

This information is linked to the workflow and patient processes. Furthermore, the patient flow and changes required in patient path should be taken into account when implementing a new technology. It has to be explained what kind of staff is needed, and whether the existing staff can be trained. The use of technology could be monitored in order to clarify if the new technology modifies the quality of patient flow.

Describe the features of “structure” topic:

- Decentralization or centralization of technology (e.g. the location of the use of the technology that could be vary between different countries);
- Costs (e.g. budget impact of the implementation of the technology for the payers or analysis of additional costs). In particular, this aspect will be done with economic domain.

Describe the "management topic":

- Management of the problems and the options attached to a specific technology (e.g. resources management, co-ordination, definition of objectives, monitoring and control, analysis of the activity and results)
- Criteria for the assessment of management tools related to a specific technology (e.g. check of the increase appropriateness level produced by new technology).

The "Culture" topic consists of the options and standard for organization, personnel and patients (e.g analysis of the positive and negative interpretations of the new technology by different professional groups).

The second step consists of an identification of the research problems and questions for the technology to be assessed: the organizational analysis should deal with the overall policy question and the organisational set-up.

The research strategy should collect the relevant studies focusing on the organisational aspects in order to make a systematic search of the evidence; if there are no systematic reviews or meta-analysis, primary studies should be used.

To reduce publication bias, the research strategy should be steered to obtain all available evidence, a systematic classification of available evidence, its objective assessment and a summary analysis (e.g. meta-analysis). An appropriate research strategy includes the following methodological questions:

- clear definition of the objectives;
- clear description of the strategy used;
- clear description of the inclusion and exclusion criteria used;
- brief summary of the characteristics of all included and excluded studies;
- methodological quality evaluation of primary studies and description of the criteria used;
- clear result presentation of the included studies (with statistical figures).

It is difficult to find organizational scientific evidence produced from systematic reviews or meta-analysis and to identify relevant data sources. For this reason, incomplete and partial revisions are often produced.

To reduce these risks, the published literature, the grey literature, hand searching of journals, contacting experts and scanning reference lists of relevant papers should be included.

The literature search can be performed in different database as listed in Appendix 8. The database of GIN recommendations, the registers and international, national and regional routine collected statistics are also the important sources of information. Conference proceedings and manufacturers' reports can also provide answers to some organizational points.

From experience gained in Joint Action 1, we observed that these databases are often unsuitable to collect all available evidence. To complement the low level of data available in the literature, other methods of gathering information are recommended, such as the "individual methods" (questionnaires, face-to-face interviews, case-study analysis, Delphi method, failure analysis) and the "Group-based method" (focus groups, concept mapping, consensus panels, nominal group techniques). The questions could be posed verbally or by using standard interview forms (e.g. telephone interviews) or in written form as postal questionnaires. It would be reasonable to administer the questionnaires to all Eunethta partners in order to receive evidence focusing on the organizational aspects by each country.

2. Data extraction

Data extraction should take into account the strength of the study design, the performed analyses, the target population, the interventions and outcomes measured.

The data from the literature review results could be structured and directly related to the research questions posed. In particular, the data (especially of quantitative studies) that should always be extracted are: data that identify the types of the studies (such as 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.

In this phase, the use of tables (such as the following table), might aid the collection of information.

Authors (year)	Types of study	Interventions	Outcomes	Notes

To facilitate the information pool, data extraction could be shared among several authors.

For the selection of articles, the following inclusion criteria could be considered:

- To include all HTA reports
- To include all economic studies (in case they contain information about work flow, patient flow, investment needed, etc)
- To include articles where the abstract refers to organizational issues
- To include studies which carry out to detect the acceptability of the technology among professionals.

3. Quality assessment of the studies

We are not aware of quality criteria for articles which consider the organization of health care. In general, it has been desirable to evaluate the technology transferability. The organizational impact assessments are linked to the organizational context in which the technology works. The literature results are not completely transferable. In this case, the study's conclusions can be considered as the assumptions to be confirmed in your organization.

4. Analysis and synthesis

The other step of the process is the narrative synthesis of the results. Quantitative data synthesis could be obtained by meta-analysis that combines the results of the included studies. Qualitative evidence synthesis may be carried out through the tabulation of study characteristics and their results.

5. Results

It would be desirable to:

- describe the interpretation of the findings in all the result cards of the domain;
- discuss the significance of methodological issues that may affect the interpretation of results, e.g. access to information, quality of information, conduct of studies, biases;
- write the indications for further researches;
- expose the related questions;
- not provide recommendations.

6. Internal review among different authors

It might be necessary to carry out an internal review process in order to harmonize the result cards and ensure coherence of the results in the domain. In this phase, the Primary Investigator plays an important role of coordination between authors and should be responsible for the final editing (if necessary). In the past

experience of the Joint Action 1, the PI of the organizational domain had to make some final changes, such as:

- re-ordering some text for consistency between answers
- editing throughout to remove words and phrasing which imply a recommendation
- editing throughout to remove statements which are not substantiated either by the literature or other data sources
- editing for improving clarity.

At the end, it would be useful to write a brief summary of the main results of the organizational domain, keeping them clean from all interpretation and judgment.

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2.12 Domain specific issues: Social aspects of the technology (SOC)

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

Aim

The aim of chapter is to provide HTA Core Model domain team members with practical guidance on a list of issues which have to be taken into account when developing the domain content.

Evidence base

HTA Core Model Handbook (last version available)

Practical guidance

The assessment process may differ with respect to each technology. The following phases may need to be gone through in the following order and to the extent that is necessary to find answers to the relevant issues:

1. Take your literature selection and screen for the Assessment Element(s)

- Search for literature reviews, or if no literature reviews are available
- Consult health care professionals and content experts (proxy informants) for their opinions
- Document methods followed

The literature research can be performed in different databases as listed in Appendix 8.

2. Provide results (even descriptive) that can answer the AE(s)
3. If there is no answer, state it
4. If you miss some major social aspects and no study reported them, state it in the discussion (generally or in the AE comments sector)

Quality assessments should evaluate:

- 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)

Bibliography

EUnetHTA WP8 – HTA Core Model 2.0 – www.corehta.info (access January 30 2015)

2.13 Domain specific issues: Legal aspects of the technology (LEG)

[methods to develop domain content]

Aim

The aim of the methodological guidance for the LEG domain is to provide HTA Core Model users with a brief list of issues on legal evaluation which have to be taken into account when answering the relevant assessment elements and, guide users through a step-by step procedure which will facilitate respect of legal normative and human rights.

Evidence base

The evidence sources for the legal domain differ from those of biomedical evidence .

As the highest level of evidence written law is seen as a fact. There are several levels of written law, like

- EU legislation
- National legislation
- EU recommendations
- Federal national law

The second level of evidence can be seen as the interpretation of the existing regulations

- Detect differences between different legislation levels
- Search for legal literature

Further sources of evidence

- Medico-legal literature: search for legal aspects in medical databases
- Use the commonly developed literature search of the HTA to detect legal issues
- Interpret existing (local) legislation (i.e. in terms of supporting or hindering the implementation of the intervention)

Practical guidance

Contributors chosen to develop this domain should have a legal background or experience in the subject matter. The process includes three steps:

1. Recognize relevant legal questions 2. Identify the needs of national adaptation 3. State the level of transferability of the results in the conclusions

Bibliography

EUnetHTA WP8 – HTA Core Model 2.1 – www.corehta.info Legal aspects

Appendix 1. Topic Notification and Selection Procedure Form

Core HTA Topic Notification Form

Introduction

The purpose of this form is to collect notifications (i.e. identification and transmission) information for interventions to be selected for assessment in a full Core HTA as part of the JA2 WP4 process.

Topic Selection Procedure

This procedure is based on the experience from JA1 and the first two core HTAs of JA2.

Each participant can submit one or more proposals using the Topic Notification Form (one for each technology notified), sent by Agenas to all EUnetHTA members and to the Stakeholder Forum members.

A list of notified technologies from the previous Topic Selection Procedures (JA2 Core HTA 1 and Core HTA 2) is also available so that some technologies can be notified again.

If you are not sure on some requested data, please write NA (not applicable).

Proposals will be collected by Agenas team, deadline no later than **August 15th**

Once Agenas has received proposals:

1. A consolidated list of technologies will be made available after a face assessment to identify vague notifications and notifications which appear to contain mistakes.
2. Each WP4 Partner will express their preferences for 3 technologies of interest to them, giving them a scores from 3 (the most important) to 1 (the least important)

   (The significance of the term “importance” will be left to individual originators of the form).
3. The resulting scored consolidate list will be shared and
   a. If there is a clear “winner” (a technology which has scored more 3s that the others), this will be selected as a working topic with the runner up(s) as reserve(s);
   b. If there is no clear winner (there is more than one technology with the same 3 scores), the scored sheet with the top scoring technologies will be circulated for a quick (3 days) further round of voting until a clear winner emerges

Source of topic proposal:

Country	
Institution	
Name of respondent	
e-mail	
Date of proposal	

Please identify one candidate technology for assessment with the HTA Core model On-line (generic and commercial name if applicable):

_____

_____

N.B. Only specific technologies will be considered. Notifications of broad categories of technologies (e.g. genetic tests for cancer, in vitro diagnostics of infection etc) will not be considered and the form will be returned to the originator with a request for more specific information.

Please indicate the type of technology [1]

☐ **Diagnostics** ☐ **Medical or surgical intervention** ☐ **Screening**

☐ **Pharmaceutical**

Please provide the Title of the proposed assessment topic:

_____

_____

_____

Proposed Topic is presented as "alert" in POP database Yes/No

Please indicate why there is need to assess this healthcare technology (select all that apply):

- ☐ Potential clinical benefits
  (e.g., reduced number of heart attacks, strokes, or emergency room visits)
- ☐ Potential non-clinical benefits
  (e.g., improved patient satisfaction, shorter hospital length of stay)
- ☐ Utilization pattern
  (e.g., current use is a deviation from recommended use, inconsistent use)
- ☐ Budget impact on health care system
- ☐ Potential harm issues
- ☐ Ethical issues
- ☐ Other. Please specify _____

Which overall assessment question (s) should be answered by the Core HTA in order to contribute to the solution of the problem that you are describing? *Please limit to 100*

[1] Limited to Core Model ® applications available

words per question and define the questions as clearly as possible. Ideally questions should be structured as a PICO question.

What is the specific illness/condition/public health issue that is being targeted by this healthcare technology? *Please limit to 100 words.*

Describe the burden of the illness/condition/public health issue for patients AND the healthcare system. Please think of the burden in terms of (1) morbidity rates; (2) mortality rates; (3) sickness episodes; (4) number of healthcare providers involved, (5) costs for the Health Insurance or the public sector; etc. *Please limit to 500 words.*

Describe whether there is inappropriate variation in practice in dealing with this illness/condition/public health issue across your country or Europe. *Please limit to 100 words.*

Describe the type of the population affected (gender, age, subgroups of patients being targeted). *Please limit to 100 words.*

Describe any other stakeholder who may be affected by any policy change about the specific technology. *Please limit to 100 words.*

Describe the COMPARATOR (s): current standard of care of this illness/condition/public health issue or current practice. *Please limit to 100 words.*

Describe the current funding policy of this intervention and the comparator. *Please limit to 100 words.*

Indicate whether there is already evidence with regard to the proposed research topic. *Please limit to 100 words and include references.*

Indicate which data are necessary for this assessment (if the data exists, please indicate the extent to which the data is exploitable; if data not available, indicate how it would best be collected). *Please limit to 100 words.*

Please, describe any other factors important in the process of refining your topic proposal. *Please limit to 100 words.*

Place and date **Signature**

Appendix 2. Selection form for notified technologies

Introduction

The purpose of this form is to collect preferences for interventions to be selected for assessment in a full Core HTA as part of the JA2 WP4 process.

Topic Selection Procedure – The story so far

This procedure is based on experience from JA2 Core HTA 1 & 2 topic selection process and the former JA1.

Agenas sent the *Core HTA Topic Notification Form* on *DATE* to all EUnetHTA members and partners, including WP4 SAG and DG Sanco, with a comeback deadline on *DATE*. An electronic procedure was used through a specific webform in the EUnetHTA intranet (for EUnetHTA members) while a doc form was used for WP4 SAG and DG Sanco).

Once the completed forms were received, Agenas carried out a face assessment and deleted vague notifications and notifications which appeared with insufficient information.

The consolidated list of technologies is at "***WP4 Core HTA XX Consolidated List of Proposed Technologies.xls***".

Next Steps:

1. The consolidated list will be shared with WP4 Partners and WP4 SAG.
2. Each WP4 Partner and WP4 SAG should express their preferences for 3 technologies of interest to them, giving them a scores from 3 (the most important) to 1 (the least important). *"Important" means important to your agency or body at the time of notification and voting. If your agency has a national remit, then it's national importance.*
3. The resulting scored consolidated list will BE shared, and:

a. If there is a clear “winner” (a technology which has scored more 3s that the others), this will be selected as a working topic with the runner up(s) as reserve(s). No SUMRANK will be done (i.e. no aggregate scoring to define rank).

b. If there is no clear winner (there is more than one technology with the same 3 scores), the scored sheet with the top scoring technologies will be circulated for a quick (3 days) further round of voting until a clear winner emerges.

All lists of notified technologies will be available for information, to facilitate collaboration amongst notifiers and to form the basis for further selection.

Instructions:

1. Identify your choice of the 3 interesting technology in the file

WP4 Core HTA XX Consolidated List of Proposed Technologies.xls

2. Rank them in order of importance* (3 is the most important) in the table below:

Score	***Technology (see column B on the excel sheet)***
3 (most important)	
2 (important)	
1 (least important)	

3. Return this sheet with your choices and scores to:

PROJECT MANAGER NAME (EMAIL)

by DATE and no later. Late arrivals will be discarded.

**"Important" means important to your agency or body at the time of notification and voting. If your agency has a national remit, then it's national importance.*

1558

1559 ## Appendix 3. Stakeholder Involvement Template (Project Leader overview)

WP4 JA2 **Date:** ***Project Leader:***							
Responsible of communications between stakeholders and working group :							
Stakeholder	**C.O.I.***	***Purpose of STK involvement*** *(please specify Project Phase)* ➢ Topic Selection ➢ Prioritization ➢ Scoping ➢ Core Protocol validation ➢ Core Draft validation ➢ Final report	**Methods of STK involvement**	**Comments received/** **Answer received, but no comments/Date**	**Action taken** *(Author reply)/***Date**	**Stakeholders Involvements End Satisfaction** *(to be filled at the end of the project)* 1 Excellent 2 Good 3 Poor	**Stakeholders' Comments** *(to be filled at the end of the project)*
Patient and healthcare consumer organisations *Name/Contact:*							
Healthcare providers (professionals and hospitals) *Name/Contact:*							

Payers *Name/Contact:*							
Industry *Name/Contact:*							
Others *Name/Contact:*							

Stakeholders not considered *(specify name)*	**Why**
Working Group Satisfaction of Stakeholder involvement process *(to be filled at the end of the project, report only total figures)* 1 Excellent 2 Good 3 Poor	
Final Working groups Comments on Stakeholder involvement process *(if any)*	

1560 *All Stakeholders involved must sign a Conflict of Interest Declaration (C.O.I.)

Appendix 4. Survey for Manufacturer; Survey for WP4 Partners

SURVEY FOR RETRIEVING INFORMATION ON THE USE OF HEALTH TECHNOLOGY IN EUROPEAN COUNTRIES

EUnetHTA JA2 WP4 Editorial Team developed this questionnaire for a European collaborative health technology assessment of _____.

The questionnaire only asks about some aspects of the health technology and comparators under assessment.

Answer to all questions is not required by the survey but PLEASE provide as much information as possible.

If you have any question, please do not hesitate to contact WP4 Lead Partner official contact (Nicola Vicari vicari@agenas.it)
Thank you!

Personal Information

1. Country *This question is required.

2. Institution *This question is required.

3. Name of respondent *This question is required.

4. e-mail *This question is required.

Survey for Manufacturer

CUR and TEC Domains

Example:

1. **In which EU countries, and when, do you market your health technology (according the scope of this assessment)?**
2. **In which EU countries your health technology is reimbursed by the National Health Service? Please include information on co-payments or other information regarding reimbursement, if applicable.**
3. **In which EU countries your health technology is used as primary screening or diagnostic or therapeutics method?**
4. **What qualification, training and quality assurance needed for staff and laboratory used your health technology?**
5. **What kind of equipment and supplies required?**
6. **How much time has to be allowed for shipping the samples (in case of medical tests for screening)?**

We need medical test instructions for use, patients' information leaflet and CE mark document, please send us scanned by e-mail, thank you.

EFF and SAF Domains

ECO Domain

Example

Are there price lists for health technology (e.g. from some manufactuerer/countries) available? If yes can we have them, thank you?

SOC Domain

Example

1. **Do you have any Data - Qualitative study – Report about patients' acceptability, satisfaction/compliance, opinions on uptake and use of health technology?**
2. **Do you have any Data - Qualitative study – Report about differences in perceptions/satisfaction/compliance with health technology due to:**
   - Gender
   - Ethnicity
   - Geographic areas (e.g. Northern European countries, Mediterranean etc.)

Socio-Economical status

ETH Domain

LEG Domain

Example

1. **Where is the market authorisation for the health technology available?**

THANK YOU!

<u>Survey for WP4 Partners</u>

CUR and TEC Domains

Example

1. **What types of screening programmes (population based or opportunistic) exist in your country, if any?**
2. **What is the target population and screening interval of the screening?**
3. **How many people are estimated to belong to the target population in your country?**
4. **What is the primary screening method fordisease assessed here?**
5. **What is the current rate of screening adherence?**
6. **If specific medical test is the primary screening method fordisease under assessment, please specify which test is used (the name and Manufacturer), thank you.**
7. **Does national guideline exist on screening in your country?**
8. **How is screening illness is currently diagnosed in your country?**

9. **How is screening illness is currently managed in your country? Please provide any algorithms or guidelines, thank you.**
10. **Which market authorization status (CE mark) has health technology in your country?**
11. **What is the reimbursement status of specific screening under assessment in your country?**

EFF and SAF Domains

ECO Domain

SOC Domain

ETH Domain

LEG Domain

Appendix 5. Stakeholders Consultation Form; Authors Reply Form on Stakeholders comments

European network for Health Technology Assessment (EUnetHTA) Joint Action 2 (2012-2015)

WP4 SAG CONSULTATION FORM

PUBLIC CONSULTATION FORM

MANUFACTURER CONSULTATION FORM

EUnetHTA REVIEWERs CONSULTATION FORM ON THE DRAFT PROJECT PLAN, DRAFT REPORT, and FINAL REPORT ON CORE HTA

Core HTA Title, ID

Name	**Organization**	**Date**

Please provide your comments in Table below, thank you.

Comment #	**Page**	**Section number**	**Comment**

References

European network for Health Technology Assessment (EUnetHTA) Joint Action 2 (2012-2015)

WP4

AUTHORS REPLY FORM on SAG CONSULTATION, PUBLIC CONSULTATION, MANUFACTURER CONSULTATION and EUnetHTA REVIEWERs CONSULTATION OF THE DRAFT PROJECT PLAN, DRAFT REPORT, and FINAL REPORT ON CORE HTA

Core HTA Title, ID

SAG Comments received from:

1.
2.
3.
.....

Answer received, but no comments:

1.
2.
…..

Public consultation received from:

1.
2.
.....

Manufacturer comments received from:

1.
2.
.....

EUnetHTA reviewer comments received from:

1.
2.
.....

Answer received, but no comments:

1.
2.
.....

Comment #	Page	Section number	Comment	Author's reply

SAG comments	Public consultation comments	Manufacturer comments	EUnetHTA reviewer comments

References

Appendix 6. Conflict of Interest Declaration Form

STATEMENT ON TERMS OF PARTICIPATION AND EXTERNAL ACTIVITIES OF EXPERTS (potential conflict of interest and confidentiality undertaking) WHO ARE INVOLVED IN EUnetHTA Joint Action 2

STATEMENT YEAR:

The undersigned,

Name:

Address Street:

Postal code:

Town/city:

Employee of EUnetHTA WP [NUMBER(s)] Partner/Associate organisation: Yes/ No

accepts to participate during years 2012-2015 in the work plan of the EUnetHTA Joint Action 2 which I've read

and

provides the following information[2] on his/her honour and to the best of his/her knowledge.

Section 1. Declaration of Interests

1a. Main professional activity

Name of the organisation[3]:

Description[4]of the activity:

Period of time (years of start-end)

1b. I carried out salaried employment for / received remuneration from the following pharmaceutical/medical device/other health-technology developing and/or producing/distributing organisation(s):

[2] Please provide details on your affiliations as far as 3 years back (and up until now) from the time of filling the form

[3] Enter 'none' if you feel this point does not apply. This also applies to subsequent items.

[4] Please provide a brief description. This also applies to subsequent items.

Name of the organisation:

Description of the activities:

Period of time (years of start-end)

1c. I acted in an advisory capacity for the following organisation(s)[5] (i.e. patient, HTA, public or private research organisations,…):

Name of the organisation[6]:

Description[7] of the advisory capacity:

Honorarium: Yes/ No

Period of time (years of start-end):

Name of the organisation:

Description of the advisory capacity:

Honorarium, Yes/ No

Period of time (years of start-end):

2. I carried out clinical studies in relation to the development of a medicine/medical device/diagnostic / procedure for the following pharmaceutical/medical device/other health technology developing and/or producing/distributing organisation(s):

Name of the organisation:

Name of the medicine:

Period of time (years of start-end):

Name of the organisation:

Name of the medicine:

Period of time (years of start-end):

3. I sat on a committee or similar advisory body for the following medical research on behalf of a pharmaceutical/medical device/other health-technology developing and/or producing/distributing organisation:

Details of the research:

Name of the organisation:

Name of the medicine:

Description of the duties:

[5] Where necessary, additional entries can be made. This also applied to subsequent items.

[6] Enter ‘none' if you feel this point does not apply. This also applies to subsequent items.

[7] Please provide a brief description. This also applies to subsequent items.

Honorarium: Yes/ No

Period of time (years of start-end):

4a. I received a personal research, study or travel allowance from the following pharmaceutical/medical device/other health-technology developing and/or producing/distributing organisation(s):

Name of the organisation:

Description of the allowance:

Period of time (years of start-end)

4b. The following pharmaceutical/medical device/other health-technology developing and/or producing/distributing organisation(s) paid for my congress expenses:

Name of the organisation:

Description of the congress:

Period of time (years of start-end):

5. I gave a presentation at meetings organised by the following pharmaceutical/medical device/other health-technology developing and/or producing/distributing organisations and received remuneration for my input:

Name of the organisation:

Description of the meeting:

Period of time (years of start-end):

6. I carried out activities or drew up advice for the following pharmaceutical/medical device/other health-technology developing and/or producing/distributing organisations in exchange for personal payment:

Name of the organisation:

Description of the activities:

Period of time (years of start-end):

7. I held a managerial position in the following institutes, where medicinal research is carried out that was funded by pharmaceutical/medical device/other health-technology developing and/or producing/distributing organisations:

Name of the institute:

Description of the duties:

Period of time (years of start-end):

8. I have financial interests in an organisation involved in the field of medicines/medical device/other health-technology

Name of the organisation:

Description of the financial interests:

Period of time (years of start-end):

9. A member of my household[8] has been engaged in activities as described in items 1b-8 above

Yes/No:

If Yes, description[9]:

10. I have another interest to declare:

Yes/No:

If Yes, description:

Should there be any change to the above due to the fact that the undersigned acquires additional interests, s/he shall promptly notify the EUnetHTA Secretariat and Lead Partner of the relevant Work Package where s/he participates and complete a new declaration of interest detailing the changes. This declaration does not discharge the undersigned from an obligation to declare any potential conflicting interest(s) at the start of and throughout the whole duration of any EUnetHTA Joint Action 2 Activity activity in which s/he participates.

Furthermore, by signing this statement, I accept and agree to the following:

- Collected declarations are for information of the EUnetHTA Secretariat and EUnetHTA JA2 WP Lead and Co-Lead Partners of WP only and it is the responsibility of the EUnetHTA Secretariat and Lead and Co-Lead Partners to keep the information confidential.
- Signed declarations will be stored in electronic form, protected by password access only.
- In case of the conflict of interest being identified, the issue of handling this conflict of interest will be between the individual and the EUnetHTA Secretariat or (as relevant) the Lead Partner or Co-Lead Partner of a relevant WP. Accuracy of the conclusion is the responsibility of the individual (providing correct information) and the Lead Partner or Co-Lead Partner (as relevant). Details of such conclusions and their consequences will not be made known to any third parties other than the members of the working group/team of the respective project. The process of assessing the conflict of interest and its general outcome will be described in the final report from the project to ensure transparency of the procedures while respecting the privacy rights of any individuals concerned.

[8] Household member is a spouse, partner, or child living at the same address as the individual who signs the conflict of interest declaration.

[9] Please provide a description following the format of Items 1b-8 of the declaration. Individuals from countries where information on the 3'rd persons are legally not allowed to be provided may omit this item – indication of the legal reason of omitting this information need to be explicitly indicated.

Section 2. Confidentiality undertaking

In view of the following definitions:

"EUnetHTA Joint Action 2 Activities" encompass any meeting (including meeting preparation and follow-up), associated discussion or any other related activity of the EUnetHTA Joint Action 2 committees and governance bodies, its Work Packages, expert groups, stakeholder groups, or any other such meeting, work as an expert on assessments, and work as an expert on guidance development.

"Confidential Information" means all information, facts, data and any other matters which are indicated as confidential and of which I acquire knowledge, either directly or indirectly, as a result of my EUnetHTA Joint Action 2 Activities.

"Confidential Documents" mean all drafts, preparatory information, documents and any other material, together with any information contained therein, which is indicated as confidential and to which I have access, either directly or indirectly, as a result of my participation in EUnetHTA Joint Action 2 Activities. Furthermore, any records or notes made by me relating to Confidential Information or Confidential Documents shall be treated as Confidential Documents.

I understand that I may be invited to participate either directly or indirectly in certain EUnetHTA Joint Action 2 Activities and hereby undertake:

1. to treat all Confidential Information and Confidential Documents under conditions of strict confidentiality.

2. not to disclose (or authorise any other person to disclose) in any way to any third party[10] any Confidential Information or Confidential Document.

3. not to use (or authorise any other person to use) any Confidential Information or Confidential Document other than for the purposes of my work in connection with EUnetHTA Joint Action Work Package activities.

4. to dispose of Confidential Documents as confidential material as soon as I have no further use for them.

This undertaking shall not be limited in time, but shall not apply to any document or information that I can reasonably prove was known to me before the date of this undertaking or which becomes public knowledge otherwise than as a result of a breach of any of the above undertakings.

Place:

Date:

Signature:

[10] Third party does not include employees of the National Competent Authorities who either have employment contracts that provide confidentiality obligations or are encompassed by confidentiality obligations under national legislation on professional secrecy.

Appendix 7. Project Definition Template for Core HTA

Introduction

The purpose of this document is to facilitate the collaborative definition of the general information requested for the creation of a new project (Core HTA) in the EUnetHTA On-line Tool and Service (www.corehta.info).

The information in this document originates from the HTA Core Model Online (on March 18th 2013).

*Note: indications for fields are in **blue** text*

Project name (title): ***Required***	
Model version ***Required***	Short demo application HTA Core Model Application for Medical and Surgical Interventions (1.1) HTA Core Model Application for Diagnostic Technologies (1.1) HTA Core Model Application for Screening Technologies
Project type ***Required***	Core HTA Some information on the technology (free selection of topics) Testing / Pilot 2 / Validation 2012

Project scope

Please define the scope of the project which will guide work within all domains. Additionally, the structured information you provide here will enable the system to automatically suggest research questions in the next phase.

Scope elements:

- Technology and its intended use
- Target condition (the disease or health condition that is the target of the technology)
- Target population (usually a subgroup of those who have or may have the target condition)
- Comparison
- Main outcomes for each domain

Short name fields are used for automatic research questions. *Free definition* fields allow you to provide more details in plain text.

Technology

Technology short name ***Required***	*Give a short name for the technology. Add an optional abbreviation or acronym inside parenthesis. If multiple technologies are assessed, separate the names with a semicolon ; An example with two technologies: Acetylsalicylic acid (ASA); Ibuprofen*
Technology free definition	*Define the technology briefly and clearly enough to distinguish it from other related technologies*

Intended use of the technology	☐ Prevention ☐ Screening ☐ Diagnostics ☐ Treatment ☐ Rehabilitation
Intended use of technology free definition	*Please fill in the sentence: This technology is used for...*

Target Condition

Target condition short name	*Give a short name for the disease or health condition (of certain grade or severity) that is the target of the technology. Add an optional abbreviation or acronym inside parenthesis. If multiple conditions are targeted, separate the names with a semicolon ; An example with two conditions: Idiopathic headache (Headache); Neck pain*
Target condition free definition	*Define briefly the target condition (disease or other health condition) of this assessment*

Target population

Target population group	☐ Patients who have the target condition ☐ Suspected health condition ☐ Possible future health condition ☐ Healthy and/or asymptomatic people
Target population sex	☐ Any ☐ Male ☐ Female ☐ Other (please specify)
Target population age	☐ Fetuses ☐ Any age except fetuses ☐ Specific ages (please specify)
Target population further details	*Give a further refinement of the target population (if necessary). Examples: 'in office work', 'of oriental origin' or 'with myopia' (where myopia is a co-morbidity, not the target condition)*
Target population free definition	

Comparison

Comparison	☐ Placebo ☐ Not doing anything (e.g. waiting list) ☐ Specified other technology / usual care (please specify)
Comparison free definition	*Define briefly the technology or strategy to which you want to compare the technology under assessment*

Outcomes

Outcomes free definition	*Provide here an overview of the main outcomes or areas of interest for this project, in order to ensure overall clarity of the project scope. You are encouraged to consider each domain separately, but also to avoid too many details, as those can be further defined in subsequent phases of protocol design.*

Project Metadata

Metadata helps to classify your project and its results and makes it easier to find it when searching the database. Filling in the metadata is only required when moving from phase 2 to phase 3, so you can skip this part if you are in the early phases of your project.

You can use e.g. NCBO BioPortal to search for suitable terms, codes and keywords. The system won't verify the correctness of the terms, codes or keywords you enter.

Technology

Technology MeSH terms	*Separate terms with a semicolon;*
Technology ATC codes (for pharmaceuticals)	*Separate terms with a semicolon;*
Technology free keywords	*Separate terms with a semicolon;*

Target condition

Target condition MeSH terms	*Separate terms with a semicolon;*
Target condition ICD-10 codes	*Separate terms with a semicolon;*
Target condition free keywords	*Separate terms with a semicolon;*

Comparison

Comparison MeSH terms	*Separate terms with a semicolon;*
Comparison ATC codes (for pharmaceuticals)	*Separate terms with a semicolon;*
Comparison free keywords	*Separate terms with a semicolon;*

Appendix 8 – Useful Sources and Databases

- Pubmed,
- Embase,
- Cochrane Library all databases,
- Agency for Healthcare Research and Quality (AHRQ)
- Australian Safety and Efficacy Register of New Interventional Procedures
- Technologies in Health (CADTH)
- Health Canada
- NIHR-HTA Database (INAHTA)
- Medical Services Advisory Committee (MSAC)
- National Coordinating Centre for Health Technology Assessment (NCCHTA)
- National Institute for Health and Clinical Excellence (NICE)
- NHS Quality Improvement Scotland (NHS QIS)
- Trip Database
- CINAHL
- Database of Dissertational Abstract
- Scirus database
- Emerald Library,
- Science Direct,
- Education Resources Information Center
- OAlster Catalogue

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).