Joint Action on HTA 2012-2015

Procedure Manual for rapid REAs of pharmaceuticals

Date: Dec 2015

Was developed by Work Package 5 - Applying the HTA Core Model for Rapid Assessment for national adaptation and reporting

WP5 Lead Partner: Dutch National Health Care Institute

Version log

Version number	Date	Name (Initials)	Comment
V1	20/12/2012	LB	V1 was sent to WP5 members for comments (consultation period: 20 dec 2012 – 31 Jan 2013)
V2	15/03/2013	SW	Comments from WP5 members were processed and alterations were made based on the discussion at the first WP5 JA2 meeting in Diemen in February 2013 V2 was sent to the WP5 Stakeholder Advisory Group (SAG) for consultation (consultation period: 18 March 2013 – 5 April 2013)
V3	27/05/2013	LB	Comments from the WP5 Stakeholder Advisory Group and additional comments from WP5 members were processed. Alterations based on these comments were incorporated. V3 was sent to EUnetHTA secretariat for publication.
V4	01/04/2015	SW/KLI/DSA	Graphics and timelines for the pilot processes were updated. The procedure for using the submission file template and its content was adapted.
V5	30-11-2015	EVB/KLI	Final version for JA2 (integrated procedural text which was taken out of model, and specified different roles).

Table of Contents

Acronyms – Abbreviations

A	Stands for Assessment
C	Stands for Consultation
CHMP	The Committee for Medicinal Products for Human Use
CT	Coordination team for the pilot project
DTC	Description and Technical Characteristics Domain
EMA	European Medicines Agency
EPAR	European Public Assessment Report. Scientific assessment report produced by EMA
GRADE	The Grading of Recommendations Assessment, Development and Evaluation
HPCU	Health Problem and Current Use domain
HTA	Health Technology Assessment
JA	Joint Action
JA2	Joint Action 2
MA	Market Authorization
P	Stands for Project Plan (Protocol)
PICO	Abbreviation used for scoping: P=population, I=intervention, C=comparison, O=outcome
PMAH	Prospective Marketing Authorization Holder
R	Stands for Review
REA	Relative Effectiveness Assessment
SAG	Stakeholder Advisory Group. In this context the WP5 Stakeholder Advisory Group nominated by the EUnetHTA Stakeholder Forum
WP	Work Package

1. Introduction

1.1. Objective of this procedure manual:

This procedure manual guides the production of Rapid Relative Effectiveness Assessments (REAs) of pharmaceuticals in Work package 5 (WP5) Strand A.

1.2. Background information on WP5 JA2:

EUnetHTA Joint Action 2 (JA2) is a joint action between the European Commission and Member States. It aims at bringing collaboration to a higher level resulting in better understanding for the Commission and Member States of the ways to establish a sustainable structure for HTA in the European Union. EUnetHTA JA2 builds on the earlier EUnetHTA Projects 2006-08, 2009-2012 and several other European projects.

The aims of the WP5 of EUnetHTA JA2 are to:

> 1) Test the capacity of national/local HTA bodies to collaboratively produce structured rapid core HTA information on pharmaceuticals (Strand A) and other medical technologies, such as medical devices, surgical interventions or diagnostics (Strand B);

> 2) Test the application (translation) of those collaboratively produced HTAs in the national/local context;

> 3) Develop and test the models and tools as well as production processes to support collaborative and national/local production.

Testing and piloting collaborative production

A total of 6 pilot assessments on pharmaceuticals containing rapid HTA information based on structured core information from the HTA core Model® for Rapid Relative Effectiveness Assessment of pharmaceuticals will be collaboratively produced.

A schematic overview of the organisation of the process of the pilots' production is included in Figures 1, 2 and 3.

One organisation will serve as authoring institution (first/lead author), whereas a different organisation will be selected as co-authoring institution. A pool of dedicated reviewers originated from 2-5 different institutions will take part in an extensive reviewing process.

Transferring a rapid HTA or parts of the information into local (e.g. national or regional) HTA reports

All WP5 members are expected to put forth an effort towards transferring rapid HTAs or parts of the information produced within WP5 into local (e.g. national or regional) HTA reports. This should result in about 20 national/local reports based on the pilot assessments. Information on the current level of uptake can be found here: http://www.eunethta.eu/national-uptake .

Development and testing of models and tools as well as production processes to support collaborative and national/local production

During joint production of pilot assessments, the following products will be tested and further developed based on the experience gained:

- o the "HTA Core Model® for Rapid REA"

- o templates for calls for collaboration, Project Plans, rapid assessments

o   the template for manufacturer's submission file developed by WP7

WP7 is developing a manufacturer's submission file template based on the Core Model with a special focus on rapid assessments. WP5 will be testing this template in the pilots and provide input for further development. The manufacturer is invited at the beginning of a pilot process to complete and submit this file. All information that has been submitted in the submission file can be used upon the pilot team's decision within the assessment report.

1.3. Objective of the pilots

The purpose of the pilots is to produce rapid assessment reports based on cross-border collaboration, to test the usability of the model for rapid REA including guidelines. Other relevant outcomes of the pilots are:

- the authors' opinions/appreciation about cross- border collaboration in producing a REA report.
- the duration of the assessment
- the workload (in terms of working hours)
- the WP5 members' perceptions about the format of the assessment report, adaptability of information into national/local purposes, and its readability.

2. Project Management

2.1. Process of rapid assessments

A schematic overview of the organisation of the process of the pilots is included in Figure 1 (general overview), Figure 2 (scoping phase) and Figure 3 (assessment phase). However, it should be read as an ideal picture due to the high possibility of divergence (e.g. doing pilots with products that are already on the market).

In addition, the goal is to begin the scoping phase 180 days before the CHMP opinion is given. However, the timelines remain uncertain as the time from the start of the MA process (the assessment itself without pre-submission phase) to CHMP positive opinion is maximum 210 days (without clock stop), or if accelerated, the assessment phase is shortened to as few as 150 days. Therefore the start of the scoping phase at this time may not be possible in all cases, and must remain the 'ideal' picture. For each pilot, timelines are discussed with the company applying for market authorisation during the scoping phase and included into the Project Plan before the start of the Assessment phase.

The different steps and timing are also presented in Table 1.

Figure 1: Schematic overview of the organisation of the process of the pilots - General Overview
It should be noted that these graphs represent the ideal picture; however, divergence is very possible for specific joint REA's
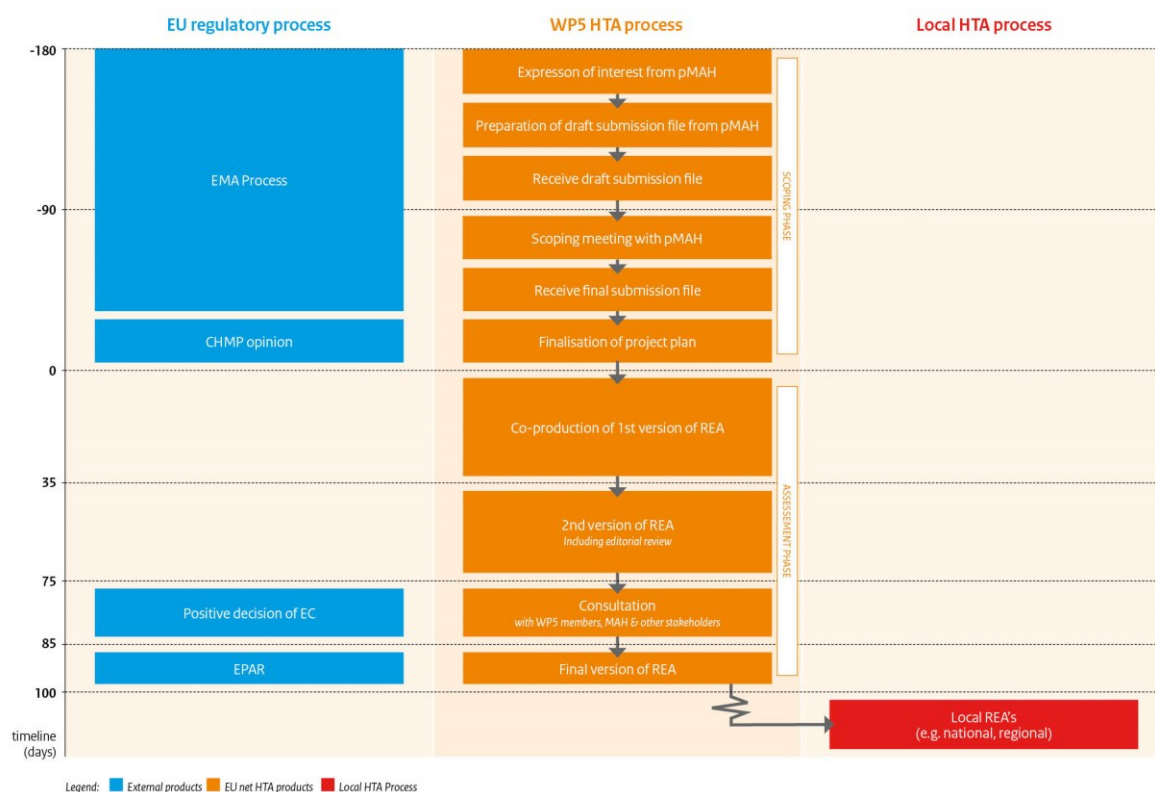
Figure 2: Schematic overview of the Scoping Phase
It should be noted that these graphs represent the ideal picture; however, divergence is very possible for specific joint REA's
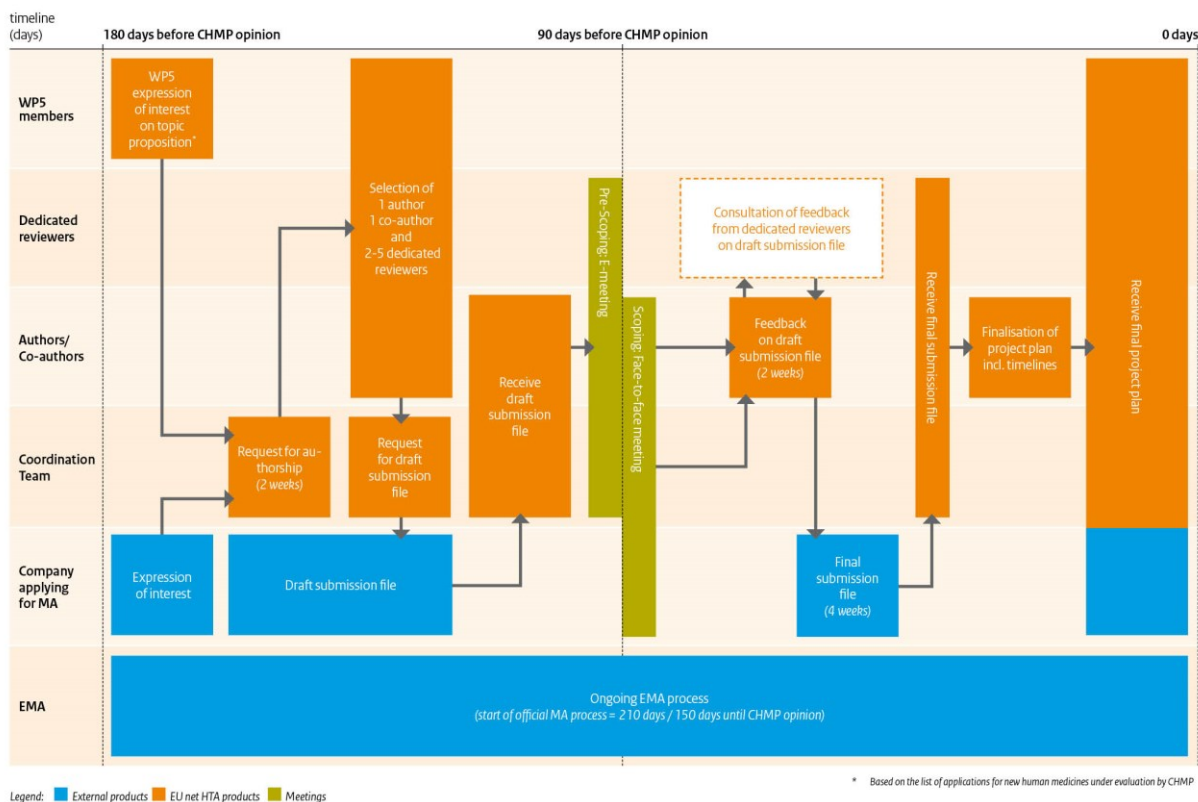

Figure 3: Schematic overview of the Assessment Phase
It should be noted that these graphs represent the ideal picture; however, divergence is very possible for specific joint REA's
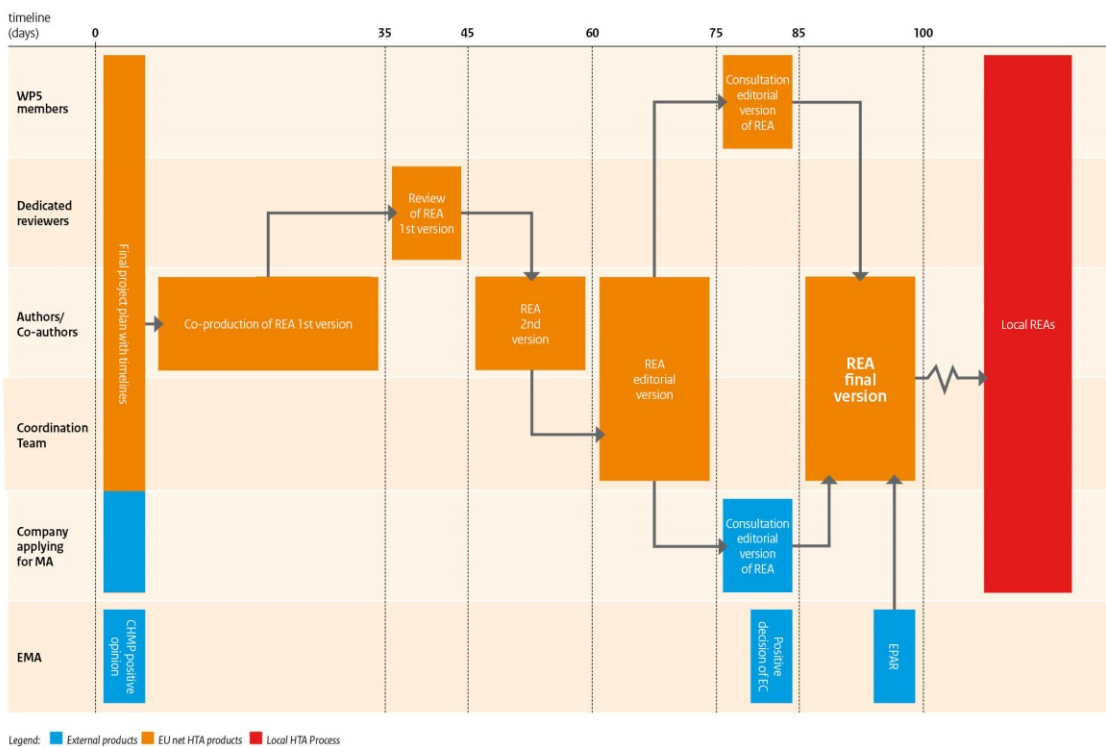
Table 1. Schedule of the pilots – Scoping Phase

Scoping				
Start [days]	**End [days]**	**Activity**	**Target group**	**Parties involved**
-	-	Letter of Intent	CT	Manufacturer
-	-	Request for authorship	WP5 Strand A members	CT
-	-	Selection of authors and dedicated reviewers	Authors, Reviewers	CT, WP5 Strand A members
-	-	Request for draft submission file	Manufacturer	CT
-	-	Draft submission file	CT, Authors	Manufacturer
-	-	Draft Project Plan	CT, reviewers, manufacturer	Author/Co-author
-	-	Status of market authorisation (indication of positive opinion or CHMP 1st report)	CT	Manufacturer, (EMA?)
-	-	Scoping e-meeting	Reviewers, (CT)	Author/Co-author (CT)
-	X	Scoping face-to-face meeting	Manufacturer	Author/Co-author (CT)
-	X+14	Feedback on draft submission file including possible consultation with reviewers	Manufacturer	Author/Co-author (Reviewers)
X+14	X+42	Final submission file	CT, authors, reviewers	Manufacturer
X+42	X+49	Final Project Plan	CT, reviewers, manufacturer	Author/Co-author

Table 2. Schedule of the pilots – Assessment Phase

Assessment phase				
Start [days]	**End [days]**	**Activity**	**Target group**	**Parties involved**
0 (0=X+49)	35	Writing first draft report	Reviewers	Author/Co-author
35	45	Review by dedicated pool of 5 review organisations	Authors	Reviewers

Assessment phase				
45	75	Writing second draft report, including editorial review	WP5 Strand A members, Manufacturer, other stakeholders	Author/Co-author, Editor
75	85	Consultation of the editorial draft report with WP5 members, MAH and other stakeholders	Authors	WP5 Strand A members, Manufacturer, other stakeholders
85	100	Final version of REA report	WP5 Strand A members	Author/Co-author
	90	EPAR available	CT, Authors	Manufacturer, (EMA?)
100	-	Adaptation of REA to the national/local reports	National/local HTA organisations/institutions	WP5 Strand A members

CT= coordination team

2.2. Pilot teams

Every team involved in the production of a pilot REA will be composed of:

- first author (from an authoring institution)

- co-author (from co-authoring institution)

- a pool of dedicated reviewers (from reviewing institutions)

- coordinating office

If appropriate and feasible other collaboration models may be tested during production of the pilot assessments.

Specific roles and tasks of team members are described below:

1) **First authors** – have a leading role in both main phases of the pilot project: scoping and production of the pilot. They are responsible for management of the pilot and together with co-authors take active part in its production.

As soon as the authors receive the draft submission file from the company applying for market authorisation, the authors start drafting the project plan. This includes information search, formulating research questions, planning methodologies and in co-operation with co-authors, creating the list of all relevant questions to be answered. They play an active role in the scoping process by arranging scoping e-meetings and consultation of the scoping with the company applying for market authorisation (in cooperation with the coordinating team). First authors send an invitation to the company applying for market authorisation, and with the support of coordinating office, they prepare and organise a scoping face-to-face meeting. First authors (with support of co-authors and dedicated reviewers) prepare feedback on draft submission file within 2 weeks after scoping meeting. In case of more complex topics, authors are encouraged to contact and consult the feedback document with dedicated reviewers at this stage. Shortly after receiving the final submission file, first authors finalise the project plan including timelines and present it to reviewers, coordination team and company applying for the market authorisation. They lead the production of the pilot REAs in a first version, take into consideration and answer the reviewers' comments and suggestions, produce the second version of the pilot REA and consult it with WP5

members and the company applying for market authorisation. They consider collected comments for production of the third version of the pilot. After receiving EPAR they check whether there are any changes in relation to the CHMP positive decision, and produce the final version of the pilot. After finalisation of the pilot REA, whenever possible, first authors should use the document for their own national/local REA.

2) **Co-authors** – play supportive role during scoping phase and take active part in production of pilot REAs.

During scoping phase they support first authors in drafting the project plan, actively participate in scoping e-meeting and consultation. Co-authors review and provide input on the feedback on the draft submission file that was prepared by authors. They accept the project plan and agree on timelines proposed in the document. Co-authors take an active part in the production of a pilot REA, and together with first authors, they consider comments and suggestions for changes collected from reviewers, WP5 members and company applying for market authorisation. After finalisation of the pilot REA, whenever possible, co-authors should use the document for their own national/local REA.

Possible work division between first authors and co-authors: Even though there is a close cooperation between authors during the production of pilot REAs, the roles of the first author of co-author should be flexible enough so as they can cooperate in a way that is the most convenient and efficient from their point of view. It is suggested to decide about division of work at the very beginning of the pilot and communicate this decision in the Project Plan. Preferably, the author and co-author should choose the mode of their action from the roles and tasks described below. There are at least two suggested ways of the division of tasks and responsibilities:

a) Workload in the production of the Domains can be divided between author and co-author, so as author will be involved in the production of two domains and co-author will develop two other. This includes data extraction from clinical trials, finding answers to the questions listed in the project plan and finally writing the report by both authors. The content produced, the selected relevant studies, risk of bias tables and data extraction by the first author would be verified by co-author and vice versa.

b) First author will be involved in the production of all domains, including data extraction from clinical trials, finding answers to the questions listed in the project plan and writing the report, whereas co-author will follow and verify every step taken by the first author during production of the report, including extraction of the data and verification of references. In case of persistent disagreement between authors, dedicated reviewers can also serve as consultants. If there is a strong divergence of opinions between producers, the reason for this (e.g. weak evidence, heterogeneity of findings, differences in interpretation) will be included in the Discussion Section of the pilot.

3) **Dedicated reviewers** – play supportive role in both phases of the project: scoping and production of pilot REAs.

Reviewers are encouraged to support authors from the very beginning of the project. They will participate in the scoping e-meeting and consultation of the draft of project plan. Whenever needed, reviewers will serve as consultants for authors and support them in the production of the feedback on draft submission file before sending the letter to the company applying for market authorisation. They accept the project plan and agree on timelines. Reviewers' major task is to make a review and verify the first version of the pilot REA and to send comments and suggested changes to authors. After finalisation of the pilot REA, whenever possible, reviewers may use the document for their own national/local REA. All suggestions of the reviewers will have to be considered by authors. If authors decide to reject the proposed changes, it must be reliably justified and documented (e.g. in a table of comments)

4) **Coordinating team** (CT) – coordinates work within the pilots and between pilots.

The CT produces the work plan and working manual for piloting REAs including templates for authors and reviewers. They take active part in the topic selection process and building the pilots' teams. CT maintains the contact with the company applying for market authorisation regarding expression of interest in participation, ensures that company sends the draft submission file, informs about the positive opinion of CHMP and on the availability of the CHMP 1st report. The CT

supports authors in the scoping phase, facilitates communication within pilots' teams (organise e-meetings if requested). They facilitate the editorial review of the pilot REA and publish the final version of the pilot REAs.

2.3. Working instructions for pilot authors

Basic tools/documents for the teams to work with are:

- Model for rapid Relative Effectiveness Assessment (REA) (version 4) & guidelines on methodological issues (version 5) produced within Joint Action 1 (JA1) WP5

- This procedure manual

- Templates for doing the assessments

- Whenever possible, the online tool will be used for the pilot assessments.

Basic sources for the teams to work with are:

- Report of positive opinion of CHMP or European Public Assessment Report (EPAR)

- Submission file of marketing authorisation holder (if possible). All information submitted by the marketing authorisation holder is available to be used in the assessment report.

The instructions in this manual divide the tasks into four main phases: project planning (protocol), assessment, review and consultation. These four phases are further divided into numbered sections.

- Phase of project planning (marked with P) includes preliminary assessment of the draft submission file, scoping, search of information, formulating research questions, and planning methodologies. At this phase authors send the feedback on draft submission file to the company applying for market authorisation. The objective of this phase is to develop a final project plan, including timelines, a list of all relevant questions to be answered in the assessment and methodologies intended to be used in the assessment.

- Assessment phase (marked with A) includes finding answers to the questions using the outputs of the protocol phase, the methodological guidance in the REA Model, and the guidelines. The objective of this phase is that each pilot team of authors provides a pilot report.

- Review phase (marked with R) includes review of the assessment. The objective of this phase is to collect and address comments and suggestions for changes from dedicated reviewers.

- Consultation phase (marked with C) includes consultation of the assessment with WP5 Strand A members, company applying for market authorisation and other possible stakeholders (European Federations of Physicians and/or Patients). The objective of this phase is to collect and address comments and opinions from all interested parties.

2.4. Communication

Internal communication

Managing the drafts

The domain teams work mostly on text documents. The authors should mark clearly the changes they make in the draft document; either using the track changes option or using different colours or fonts. Only the first author has the right to accept or reject the changes to form a new draft or a complete document. Reviewers should provide their comments through a comments table.

The teams can decide whether they circulate the drafts as email attachments, or use the Document Library on the EUnetHTA Intranet site.

Brief guidance to the Document Library:

1-   Log in to the intranet from the EUnetHTA website: http://www.eunethta.eu/

2-   Once logged into the Intranet, click on the icon 'Groups'

3-   Once there, select 'WP5- Rapid HTA Pilots'

4-   Click on 3rd icon from the left: 'Document Library'

5-   Select the Folder 'WP5 Deliverables'

6-   From there, select the relevant 'Book' from those listed.

7-   Within the 'Book', the latest version of the documents are listed as hyperlinks

8-   Right click the file and 'save as'. The document can now be edited from a local computer

9-   Be sure to select the 'track changes option' from the document,

10-   When finished working on the document, return to the Book chapter and upload the latest version of the document.

11-   Then select which members to notify of the newly uploaded document.

Full process is described (with screenshots) on p. 26-30 of the Intranet user manual http://intranet.eunethta.eu/general/system/files/eunethta_intranet_user_manual_1.1_0.pdf

EUnetHTA intranet WP5 group

Relevant documents will be stored at the EUnetHTA intranet WP5 group. You can access the site by clicking the "Intranet" icon in the upper right corner of the EUnetHTA public webpage http://www.eunethta.net/. From there, you should have direct access to the WP5 Group. There is a guide for the use of the intranet: http://intranet.eunethta.eu/general/system/files/eunethta_intranet_user_manual_1.1_0.pdf

If you don't have the username and password to enter, please contact directly the Secretariat: Inge Merete-Skov [INS@SST.DK].

E-meetings

There is an e-meeting facility, Saba centra, available for EUnetHTA projects. Coordinator in ZIN will set up the pilot project e-meetings and send the invitations to the participants. Pilot teams may also use Saba centra to facilitate their own internal meetings. However, only Associated Partners (APs) can set up an e-meeting, with up to 15 participants. All partners can participate.

At the Intranet site you can find a pdf-guide for Saba Centra http://intranet.eunethta.eu/general/system/files/saba_centra_basic.swf

External communication

External communication includes companies that apply for marketing authorisation for the specific products that will be part of the pilot rapid assessments. The companies willing to participate in the pilots will be involved in the scoping phase: scoping meeting and production of scoping document. Participation of manufacturer in the scoping phase should result in production of the final submission file. In addition, 2nd version of the REA will be consulted with the company applying for market authorisation and WP5 members, before the report will be made publicly available. Because of the short timelines, there will be no public consultation for seeking further feedback for the pilot assessments. Consequently, communicating the results of the assessment

in any form, e.g. poster or oral presentation, publication in any report series or international journal is not permitted before it is discussed in WP5.

The individuals who plan on presenting the process feasibility and outcomes of the pilots in any form, either in the form of article, abstract or oral presentation, should coordinate this activity in advance with WP5.

T Topic selection and building the pilots' teams

Topics (pharmaceuticals) can be proposed based on 1) an expression of interest by a WP5 partner or 2) an expression of interest by a pharmaceutical company to have a specific pharmaceutical assessed. Further details on the identification of topic for pilots are presented in the WP5 work plan.

After collecting an expression of interest, the CT will send a request for authorship to all WP5 members. A team of one first (lead) author, one co-author and 2-5 dedicated reviewers will be selected from all members of WP5 STRAND A. Authoring organisations will be identified based on their expression of interest. In case there is more than one organisation willing to lead the pilot, selection will be made on the experience of appointed authors and co-authors and willingness of a participating organisation to take up this assessment in their national/local assessment.

Conflicts of interest will be handled according to the EUnetHTA JA2 standard operating procedure (SOP). As conflict of interest may be topic dependent, conflict of interest declarations will be collected from authors and reviewers involved in a specific pilot assessments. Authors and reviewers who declare conflict of interest will be excluded from parts of or the whole work under this specific topic. However they still may be included in work under other pilots.

If external experts are involved in a WP5 pilot, conflict of interest declarations will be collected from them regarding the topic. External experts who declare a conflict of interest will be excluded from parts of or the whole work under this specific topic. However they still may be included in work under other pilots. The conflict of interest procedure will be handled according to EUnetHTA Standard Operation Procedures (SOP).

P1 Documentation & market authorisation status provided by manufacturer

Preferably, the scoping phase of the pilot starts during the market authorisation process of the product. At this time, the first report of the CHMP is unavailable and the opinion of the CHMP is still unknown. Therefore, the basic source for the scoping phase will be a draft submission file provided by the company applying for market authorisation (prospective marketing authorisation holder). This document should provide authors with the information about the topic under assessment and will serve for further preparation of the scoping meeting. All information provided in this document can be used upon the decision of the pilot team within the assessment report.

The EUnetHTA REA submission file and the EPAR are re-evaluated by the authoring agencies for the completeness. The REA submission file is a document produced by EUnetHTA, which summarises scientific requirements for reimbursement across Europe.

- o The re-evaluation of the EUnetHTA REA submission file should focus on several critical issues:

  - ▪ The literature search provided should be repeated using the same keywords. In the case of incompleteness or diverging results, the literature search should be repeated independently. If the provided literature search is older than two years, a new search should be performed.

  - ▪ The risk of bias should be assessed independently by the pilot team and information provided in the EUnetHTA REA submission file should be appraised critically.

  - ▪ The inclusion and exclusion criteria for the literature selection provided in the EUnetHTA REA submission file should be re-evaluated for their appropriateness.

Ideally, the draft submission file is received by authors before the positive opinion of the CHMP, the company applying for market authorisation will be asked to provide at least an indication of the CHMP's positive opinion and whenever possible the first report of the CHMP. After receiving this signal, the authors start drafting the project plan, prepare the scoping e-meeting and consult first

version of the project plan with reviewers, coordination team. In case of CHMP's negative opinion, the process can be suspended by the coordination team.

If no manufacturer's REA submission file is available, or if the REA submission file is incomplete, biased or outdated, it might be decided by WP5 partners to go ahead without the REA submission file. In such a case the proposed timelines will not be realistic.

P2 *Scoping the project*

The **scope** of the project should be discussed and clearly defined in the beginning of the project.

The **first step** in a rapid REA is to specify what exactly should be assessed (e.g. the scope) following the so-called PICO structure where the letters stands for.

- Population / patients with the disease of interest

- Intervention(s), i.e. the technology under assessment

- Comparison(s), that should serve as reference

- Outcomes which encompass the endpoints for assessing effectiveness and safety

The EUnetHTA REA submission file supplied by the manufacturer(s)/marketing authorisation holder should be used as reference documents for scoping. After a scoping meeting with the market authorisation holder and the authoring agencies, the final scope of the assessment is developed and summarised in a project plan. In addition, information regarding the CHMP opinion and the 1st report of CHMP is expected to be shared by manufacturer as early as possible. As soon as CHMP's 1st report and/or opinion are available, the differences between those documents and manufacturer's REA submission file should be checked, discussed during the scoping meeting and described in the feedback document on draft REA submission file. In the case of incompleteness of the file, the authoring agencies have the opportunity to request additional information, e.g. during the scoping meeting or via e-mail or an e-meeting.

The PICO (population, intervention, comparison and outcomes) will drive the evaluation in all four domains. Population, intervention and comparison will generally be the same for all domains. However, there may be sometimes need to deviate from the scope due to e.g. a subpopulation of special interest or lacking data of the population defined in the scope.

For other relevant considerations regarding the PICO elements see the [Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals](): http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf (section 2.2).

Template to be used: Table 3 (Project Scope: PICO) of the Project Plan Template, section 3.0 Project Scope and Objectives (page 5)

Scoping should be a subject for discussion with reviewers and coordination team during the e-meeting. In addition, there should be a face-to-face scoping meeting between authors/coordinators and the manufacturer.

Within two weeks after the face-to-face scoping meeting, authors will send their feedback on the draft submission file to the manufacturer. The final submission file from the manufacturer is expected within a further four weeks and this document will constitute an incentive for authors to finalise the project Plan and plan timelines.

The final project plan including deadlines for production of the draft versions of REA, the review, consultation with WP5 members and manufacturer and finalisation of the pilot, should be sent to the dedicated reviewers, the marketing authorisation holder and the Strand A members. An annex to the project plan including confidential information (such as contact details of project team members) will only be shared with the project team (author, co-author, dedicated reviewers and coordination team).

P3 *Selecting relevant research questions*

This phase involves:

- Selecting relevant issues from the Assessment elements table of the model for rapid REA.

- Translating the selected issues (generic questions) into actual research questions (answerable questions). Answerable questions – questions that can be answered in the specific, topic-depended context

Assessment elements in the HTA Core Model® for rapid REA are labelled as 'mandatory' or 'non-mandatory'. The label can differ according to the type of technology e.g. an element that is 'mandatory' for screening technologies may be 'non-mandatory' for pharmaceuticals. In general, the 'mandatory' elements are likely to be relevant for all assessments of a certain type of technology. The 'non-mandatory' elements may be relevant for specific assessments only.

'Mandatory' assessment elements have to be considered by the authors; if they do not wish to provide an answer to 'mandatory' elements, they need to provide justification. 'Non-mandatory' assessment elements can be included in the assessment, based on the experiences and preferences of authoring agencies; if authors chose to exclude these elements, they do need to be provide justification.

For a detailed explanation of how to proceed see section 2.4 of the HTA Core Model.for Rapid REA:
http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf .

Examples from the pilot of "Pazopanib for the treatment of advanced renal cell carcinoma"

In "*Health problem and current use of the technology*" domain, the issue "*What are the known risk factors for the condition*?" was translated into a research question "*What are the known risk factors for acquiring advanced and/or metastatic renal carcinoma?*".

An issue in the *Safety* domain "*How safe is the technology in relation to the comparator?"* was translated into four research questions:

- *What are the adverse events of pazopanib in renal cancer in comparison with the tyrosine kinase inhibitor sunitinib?*

- *What are the adverse events of pazopanib in renal cancer in comparison with bevacizumab (first line)?*

- *What are the adverse events of pazopanib in renal cancer in comparison with interferon-alfa or aldesleukin (first line)?*

- *What are the adverse events of pazopanib in renal cancer in comparison with the tyrosine kinase inhibitor sorafenib (second line)?*

Template to be used: Table 5 (Assessment elements, translated research questions) of the Project Plan template, section 4.0 (page 7),

P4 *Plan for methodologies of pilot assessments*

In this phase the authors should plan and report the methodologies to be used in the assessment phase, within particular domains. The authors do not need to provide a plan for every single research question separately, but rather a more general plan on domain level. The methodology section in the Model, and the WP5 guidelines, are the guiding documents for this task:

http://www.eunethta.eu/outputs/new-application-hta-core-model-hta-core-model-rapid-relative-effectiveness-assessment-pharma

It is not always possible to anticipate all methodological issues in the planning phase. If there is a need in the assessment phase to deviate from this plan, this should be reported in the methods section. No changes should be made to this plan afterwards.

Not all research questions require a thorough systematic review, and in some research areas there are no established quality assessment criteria for information, e.g. for some of the following research questions, a descriptive summary will be the most appropriate method to be used, i.e.: What is the target population in this assessment? (A007); What is the marketing authorisation status of the technology? (A0020). This should be also reported for transparency.

For more details see section 4.0 in the Project Plan template.

Template to be used: ***Table 4a (Project approach and method) of the Project Plan template, section 4.0 (page 6)***,

P5 *Compiling the final Project Plan*

This phase should result in the compilation of the final Project Plan by summarising steps P2-P4 in a draft **Error! Reference source not found.**. This draft will be reviewed by the selected pool of dedicated reviewers. Comments received will have to be taken into account by the authors prior to the compilation of the final Project Plan.

Comments and answers as well as the final Project Plan, including deadlines for production of the draft versions of the rapid assessment, the review, planned consultations with WP5 Strand B members, clinical experts, manufacturer(s) and other potential stakeholders have to be published within 10 working days after the end of the public consultation on the EUnetHTA homepage.

An annex to the Project Plan, including confidential information (such as contact details of project team members) will only be shared with the assessment team (author, co-author, dedicated reviewers and coordination team).

A6 *Assessment phase*

Template to be used: the Pilot Assessment Template.

In this phase authors have their project plan completed (phases P1-P5). They have prepared the list of research questions and a plan of methodologies to be used. Now, they enter the actual assessment phase.

One **assessment element** represents one research question and the meta-data that describes its relations. Instead of doing a single search and a single report, the authors produce four **domain reports**, which contain the answers to the research questions of the assessment elements of each domain. Next to this, a summary is produced.

Domain reports

Domain reports are templates which contains fields for:
*   the research questions,
*   the answer itself (the results),
*   a discussion section (if deemed necessary)

Writing instructions for the domain reports

Name of the field	Content
	The 5 digit identification code of the assessment element
Research question	Copy the research question from Table 5 in the project plan
Methods	In this section you should report the methods that you actually used for answering the research questions. • Describe how the pilot team shared the work • Describe the inclusion/exclusion criteria you used for selecting studies. Provide a flow chart for study selection. • Describe whether this is a systematic or unsystematic review or whether you decided to cite recent good quality report. • Describe if you did own research: survey, modelling etc. • Describe the quality assessment criteria you used. Provide a quality rating of the studies. • Provide the main characteristics of the studies included. • Describe the methods you used to e.g. calculate new summary estimates, meta-analysis, or if you used any formal quantitative or qualitative method to synthesise data. • Provide a description of the evidence that was used, including: guidelines for diagnosis and management, evidence tables for studies included in effectiveness and safety, list of ongoing and

	planned studies, risk of bias tables, and applicability tables
Result	The reader should get an idea of the nature and magnitude or frequency of the event to occur, and the overall robustness of the evidence behind this statement. There are several ways to provide this information. In many answers plain text is sufficient; in others an evidence table would be illustrative to add. Some teams may like to use GRADE or other instrument to provide overall view of the results. Mark citations in the text in the form of: [Surname of first author Year]. **Please note that this part should only focus on results, i.e. presentation of data, not interpretation.**
Discussion	Use this field to add comments for the methods used, or the reliability of the results. a. The interpretation of the findings. b. Issues that may affect the findings (the quality of the evidence, related uncertainties and the applicability of the evidence). c. Evidence gaps and related questions.
References	Provide a list of references used to answer this research question. List them in alphabetical order. Formulate them according to the elements of citation in Vancouver style http://www.lib.monash.edu.au/tutorials/citing/vancouver.html . If there are more than one references from an author, list them in the order of publishing (most recent up). If there are more than one references from an author from the same year, list them in the alphabetical order of the title, and separate them with a, b, etc.

For guidance on how to collect and analyse data see section 2.5 (page 23) of the Model for Rapid REA of pharmaceuticals:
http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf

A7 *Summary document*

The intention of a summary document is to present a meaningful overview of the domain reports. Special emphasis is in the aggregation of data on intended (effectiveness domain) and unintended effects (safety domain) in order to assess the net therapeutic benefit.

The following, at least, should be included in this summary:
• Scope
• Introduction: description of the technology; description of comparators; description of the health problem; description of the current treatment
• Results: description of available evidence and ongoing trials; description of relative effectiveness results; description of relative safety results; description of reimbursement status and marketing authorisation status in various countries.
• Summary table of relative effectiveness.
• Discussion: discussion of potential limitations, including internal validity and applicability, of available evidence and identification of evidence gaps.
• Conclusion: conclusion for each comparator as to whether the technology is less, similarly, or more effective and safe; conclusion as to whether further research is required.

For more guidance on how to produce the summary see section 2.9 of the Model for Rapid REA of pharmaceuticals:
http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf

Template to be used: "SUMMARY OF RELATIVE EFFECTIVENESS OF [xxxx] of **the** Pilot Assessment Template.

A8 *Compiling the final report*

First author compiles the final project report with input from the coordination team (CT). One task is to screen the possible overlapping and agree about their management with CT. Some content editing is probably needed due to the overlaps, as well as technical editing. The general structure of the report is:

COVER SHEET

SUMMARY OF RELATIVE EFFECTIVENESS OF [XXX]

LIST OF ABBREVIATIONS

1   SCOPE

2   METHODS AND EVIDENCE INCLUDED

3   HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

4   DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY

5   CLINICAL EFFECTIVENESS

6   SAFETY

7   POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS

APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

APPENDIX 2. REGULATORY AND REIMBURSEMENT STATUS

APPENDIX 3. CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS

R9 *Review*

Authors of the pilot send their first version of rapid REA to several dedicated reviewers on 35th day after starting the production.
Reviewers are prepared to dedicate their time and efforts towards thorough reviewing process according to the timelines indicated in the Project Plan. They control phases of REA production (A6-A8), including check of references and data extraction, and send their comments to authors using the template for reviewers within 10 days.
Authors are prepared to process the reviewers' comments and possible suggestions for changes within next 15 days, starting from 45th day of the project. After comments are received, the authors process them, provide feedback to reviewers in the form of responses to the comments, and draft the second version. This second version of the REA also undergoes an editorial review.

On 75th day, when the editorial review and revision is complete, the pilot REA is ready for further consultation with WP5 members, pMAH and other stakeholders. (see next chapter).

C10 *Consultation*

Consultation phase starts from the 75th day of the REA production process. Authors send the second draft of the pilot REA to WP5 members, to the manufacturer and possibly also to other stakeholders indicated by CT (e.g. European Federations of Physicians or/and Patients).
All consulted parties will be made aware of the timelines beforehand, as communicated in the Project Plan, and are ready to provide their input within 10 days using the consultation templates.
Starting from the 85th day, authors produce the final version of the pilot REA and answer comments collected during consultation. Original comments received are addressed by authors and enclosed as an appendix to each pilot. As soon as EPAR is available (in case it was not available yet), the authors check whether there are any changes in relation to the CHMP positive opinion.
The final version of pilot REA, which takes into account the comments made by the consulted parties, is ready on the 100th day of process and is sent to CT for further technical and editorial amendments. At the same time authors, dedicated reviewers and other WP5 members put their efforts into adaptation pilot REA into national/local REAs.

Collecting process related data throughout the project

Data on the following outcomes of the project are to be collected by the coordinators:

- the authors´ perceptions about cross- border collaboration in producing a REA report.
- the duration of the assessment
- the workload (in terms of working hours)
- the WP5 members' perceptions about the format of the assessment report, adaptability of information into national/local purposes, and its readability.

This will be done through developing a standard evaluation form for the pilots.

Coordination team

The pilot REAs for pharmaceuticals are coordinated by ZIN. Contact details: 23

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Appendix 1: Definitions

Back up

HTA Core Model: Generic model for creating and presenting HTA information as assessment elements. A tool of EUnetHTA Collaboration.

Model for rapid REA of pharmaceuticals: a model that was developed to do rapid relative effectiveness assessments of pharmaceuticals. A rapid assessment is an assessment of a specific technology within a limited timeframe in comparison with one or more relevant alternative interventions. It can be the assessment of a new pharmaceutical launched into the market, or the (re)assessment of a pharmaceutical for a new indication or when new relevant data are available. The model for rapid REA contains four of the nine domains of the HTA Core Model (first four domains). For these domains a subset of the assessment elements of the HTA Core Model are included.

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

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

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

Issue: An even more specific area of consideration within any of the topics. One topic typically consists of several issues, but it may also contain only one issue. An issue is always expressed as a question that can be answered through answering one or more research questions.

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

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

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

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

HTA Core Model for rapid REA of pharmaceuticals: A model that was developed to conduct rapid relative effectiveness assessments of pharmaceuticals. A rapid assessment is an assessment of a specific technology within a limited timeframe in comparison with one or more relevant alternative interventions. It can be the assessment of a new pharmaceutical launched into the market, or the (re)assessment of a pharmaceutical for a new indication or when new relevant data are available. The model for rapid REA contains four of the nine domains of the HTA Core Model (first four domains). For these domains a subset of the assessment elements of the HTA Core Model are included.

Appendix 2: Assessment Elements

AE	Topic	Issue	Clarification	Importance **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening.	
				Mandatory	Non-mandatory
1. Description and technical characteristics of the technology					
B0001	Features of the technology	What is the technology and the comparator(s)?	This is relevant in all assessments. Use the descriptions of the technology and comparator(s) defined in that scope and elaborate them here in more detail. Technology may include a single device, a questionnaire, imaging or sequence of technologies. The HTA may address one or several similar technologies. Describe separately for the technology and the comparator: the type of device, technique, procedure or therapy, its biological rationale and mechanism of action; and also, describe how the technology differs from its predecessors, and the various current modifications or different manufacturers' products, especially if the differences affect performance.	M P S D	–
A0020	Regulatory status	For which indications has the technology received marketing authorisation or CE marking?	There are both international and national market authorisation systems. The systems differ between countries and are more established for pharmaceuticals than for medical devices. An overview of the status with regard to key processes, e.g. CE marking, EMA/US Food and Drug Administration (FDA) approval is recommended. In case the technology is authorised under a different process, e.g. adaptive licensing or conditional reimbursement, information should be presented. Also, information on national data and an analysis of possible discrepancies can be useful. <u>Specific to diagnostic technologies:</u> Imaging devices may require approval. Substances needed for obtaining images may require additional approval (e.g. radiotracers). In some cases, the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but in most cases, approval is obtained for diagnostic use and the test is proposed for screening without any other formal approval. <u>Specific to screening technologies:</u>	M P S D	–

AE	Topic	Issue	Clarification	Importance **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening.	
				Mandatory	Non-mandatory
			Imaging devices may require approval. Substances needed for obtaining images may require additional approval (e.g. radiotracers). In some cases the approval for primary screening is different to that for clinical use (FDA recently licensed tests explicitly for screening), but in most cases approval is obtained for diagnostic use and the test is proposed for screening without any other formal approval		
B0002	Features of the technology	What is the claimed benefit of the technology in relation to the comparators?	This issue is especially relevant in new technologies with uncertain expectations and claims of benefit. Describe the following aspects: • How is it expected to be an improvement over previous/existing technologies used for the same health problem? • The expressed objectives for the implementation of the technology in health care; what are the claimed objectives (e.g. increased safety, health benefit, accuracy or patient compliance), and is it intended to replace or to supplement existing technologies?	M P S D	–
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	Most technologies will be introduced at approximately the same time in several countries. This information is relevant for the assessment while the evidence base may change rapidly for technologies that are at an earlier stage in their development. It is also important to establish whether new versions of the technology with substantial improvements are expected in the near future. For end-users it is useful to know whether new versions or adaptations of the technology are expected in the near future. Describe the following aspects: • Is the technology an innovation? • When was it developed? • Is the technology only partially innovative (i.e. a modification of an existing technology), and in that case, is it possible to specify the degree of innovation the technology may represent?	–	M P S D

AE	Topic	Issue	Clarification	Importance **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening.	
				Mandatory	Non-mandatory
			- When was the technology introduced into health care? - Is the technology an already established one, but now used in a different way, for instance for a new indication? This issue may be less relevant for new pharmaceuticals. - Is it experimental, emerging, established in use or obsolete (implementation level)? - Is the technology field changing rapidly? - How does this technology differ from its predecessors (other technologies used for similar purposes)? - Are there new aspects that may need to be considered when applying it? - Is there evidence that the technology works (or is used) outside its current indication area or produces incidental findings that can have consequences relevant to effectiveness, safety, organisational, social and ethical domains?		
B0004	Features of the technology	Who administers the technology and the comparators and in what context and level of care are they provided?	This issue should be answered in case there is a relevant difference between the technology and the comparator. Describe the following aspects: - Which professionals (nurses, doctors, and other health-care professionals) apply and make decisions about starting or stopping the use of the technology? - Do the patients themselves, or their carers, administer the technology? - Who can select the patients, make referrals, decide to initiate the use of the technology or interpret the outcome? - Are there certain criteria (skills, function, training requirements) for the patients or professionals who will administer the technology? Describe the level of care in which the technology is used: self-care, primary care, secondary and tertiary care. If secondary or tertiary care, describe whether it is intended to be used in the outpatient or inpatient setting. Its role in the management pathway can be presented as a replacement, an add-on or for triage.	M S D	P

AE	Topic	Issue	Clarification	Importance **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening.	
				Mandatory	Non-mandatory
B0008	Investments and tools required to use the technology	What kind of special premises are needed for the technology and the comparator(s)?	This issue should be answered in case there is a relevant difference between the technology and the comparator. Many technologies require purpose-built premises, such as radiation-secured areas, Faraday cages, dressing rooms for the patient, or specific premises equipped with fume cupboards for storage and reconstitution of chemotherapy pharmaceuticals. Typical premises in primary or secondary care may differ markedly from country to country. A clear description of necessary facilities is needed instead of a general statement (e.g. to be used in hospitals only). This issue may be less relevant for pharmaceuticals.	–	M P S D
B0009	Investments and tools required to use the technology	What supplies are needed for the technology and the comparator (s)?	This issue should be answered in case there is a relevant difference between the technology and the comparator. Examples are syringes, needles, pharmaceuticals and contrast agents, fluids, bandages and tests to identify patients eligible for treatment.	–	M P S D
A0021	Regulatory status	What is the reimbursement status of the technology?	Information on national reimbursement status from different countries for the technology as well as the comparators, including key dates and anticipated licensing time frame. Information on full coverage, co-payments and coverage under special circumstances/conditional coverage is useful.	–	M P S D
2. Health problem and current use of technology					

AE	Topic	Issue	Clarification	Importance	
				Abbreviations: D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening.	
				Mandatory	Non-mandatory
A0002	Target condition	What is the disease or health condition in the scope of this assessment?	Use the target condition and International Classification of Diseases (ICD) codes defined in the **scope of the project** and consider adding details such as: description of anatomical site, disease aetiology and pathophysiology, types of disease or classification according to origin, subtype, severity, stages, or risk level and different manifestations of the condition. The following properties of the target condition are defined in separate assessment elements: risk factors (A0003), natural course (A0004), symptoms (A0005) and burden of disease for the society (A0006).	M P S D	–
A0003	Target condition	What are the known risk factors for the disease or health condition?	Describing risk factors is especially important when they suggest possibilities for primary and secondary prevention. This information may affect the choice of comparator or the appraisal of the overall value of the technology under assessment. The risk factors for acquiring the condition, and the risk factors for relapses or worsening of the condition should be reported here separately. The prevalence of the various risk factors might differ in different geographic areas and among different subpopulations.	-	M P S D
A0004	Target condition	What is the natural course of the disease or health condition?	This assessment element should provide information on the prognosis and course of the health condition when untreated. This information is relevant for appraising the overall value of the technology. It may also guide the assessment of the predicted value or effectiveness of the technology, as technologies may work differently at different stages or severity grades of the disease, and there may be a relationship between earlier intervention and better prognosis. This element should also provide information on the time lag between the onset of disease and the symptoms or other findings that eventually trigger the need of diagnostics and care.	M P S D	-

AE	Topic	Issue	Clarification	Importance — Abbreviations: D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening.	
				Mandatory	Non-mandatory
A0005	Target condition	What are the symptoms and the burden of disease or health condition for the patient?	This element should describe the patients' relevant symptoms before intervention with the technology, their severity and whether they are persistent, intermittent or undulating taking into account different stages of the disease. Patients' perceptions of the burden of the disease are not always in line with the clinical seriousness of the disease or its societal burden.	M P S D	–
A0006	Target condition	What are the consequences of the disease or health condition for the society?	Describe consequences and burden of the disease or health condition by providing information on prevalence or incidence of the disease that is prevented or treated by using the technology; disease-specific mortality and disability, life years lost, and/or disability-adjusted life years, QoL, quality-adjusted life years (QALYs).	–	M P S D
A0024	Current management of the condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	The effectiveness of an intervention may vary in populations which are diagnosed by different diagnostic pathways. A sensitive test tends to have low specificity such that there are several people who do not have the condition among the test-positive population. The effectiveness of an intervention in that population may be lower than in a population examined with a less sensitive test (but with more true-positive cases). It is important to point out possible discrepancies between guidelines and actual practice.	M S D	P

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AE	Topic	Issue	Clarification	Importance Abbreviations: D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening.	
				Mandatory	Non-mandatory
A0025	Current management of the condition	How is the disease or health condition currently managed according to published guidelines and in practice?	It is important to describe whether the technology is an add-on or a replacement for the existing management options, and what the other evidence-based alternatives are. Are there differences in the treatment of diseases at different disease stages? Deviation from evidence-based guidelines may suggest over- or under-use of the technology. Identification of practice variations due to the differences in the forms, stages or severity of the disease may imply differences in the quality of health care. Different stages of disease may call for different therapeutic procedures (e.g. aortic insufficiency is first treated with medication, and at a certain point of cardiac structural changes, an operation is preferred). Provide an overview of other treatment alternatives. Likewise, diagnostic or monitoring methods used for various diseases may vary depending on the stage of disease.	M P S D	–
A0007	Target population	What is the target population in this assessment?	Relevant for all assessments: both safety and effectiveness depend largely on the subpopulation towards which the intervention is targeted. The technology may be used for all patients with the condition, or only those in the early stages, or at a specific severity level or for those at moderate risk of having the condition. Personalised medicine divides the target population into even smaller units when targeting the intervention to specific subgroups based on e.g. genetic profile. Use the target population defined in the scope of the project, and consider adding further details and description of who defined the selected subgroups and why. Point out e.g. if certain populations should be excluded from the analysis.	M P S D	–
A0023	Target population	How many people belong to the target population?	This information can be used to give an idea of the resource requirements in general for implementing the technology. Estimates of incidence and prevalence should be provided. Estimates of likely relevant increases or decreases in the size of the target population in the future should also be included.	M P S D	–

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| AE | Topic | Issue | Clarification | Importance |
| | | | | **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening. |
				Mandatory	Non-mandatory
A0011	Utilisation	How much are the technologies utilised?	Provide national estimates for current and future utilisation rates for the indication under assessment, for both the technology under assessment and its comparators. Variations in utilisation reflect market access, sales figures, actual usage in hospital level and adherence to the use of the technology by professionals and patients. Data on current and previous utilisation reflect the phase of the technology (experimental, emerging, established or obsolete). This also has implications for the availability of evidence and the level of uncertainties. Specific to screening technologies): What is the current rate of screening adherence?	S M	P D
3. Clinical Effectiveness					
D0001	Mortality	What is the expected beneficial effect of the technology on mortality?	Report the results both in absolute terms and relative to the comparator. Mortality is the preferred, objective endpoint for assessments of life-threatening conditions. Overall mortality, disease-specific mortality and mortality due to causes other than the target disease are distinguished. Several methods are used to adjust mortality rates and survival curves, e.g. relative survival (observed versus expected survival), which can be quite misleading; and HR (derived from a statistical method comparing the median survivals in the two groups). Note that progression-free survival is not a mortality endpoint; it describes the time from the beginning of an intervention until a patient shows signs of disease progression. Overall mortality refers to all-cause mortality. It is expressed either as mortality rates (incidence in given population, at given time point and usually risk standardised), or survival (number of people alive for a given period after an intervention). Disease-specific mortality is a proportion of all-cause mortality. It should be noted that even if a given treatment reduces one type of death, it could increase the risk of dying from another cause, to an equal or greater extent. Disease-specific mortality is typically presented as rates	M P S D	–

AE	Topic	Issue	Clarification	Importance **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening.	
				Mandatory	Non-mandatory
			and as age- and risk-adjusted measures such as HR. It is a frequently used endpoint in screening trials, where it is considered to be subject to bias. Consider separately, absolute mortality (compared with placebo or waiting list) and mortality relative to the comparator. Mortality due to causes other than the target disease includes all unintended, either positive or negative effects of the technology on mortality. There may be e.g. a decrease of mortality of another disease observed or suspected; or increased mortality due to accidents or hazardous medical interventions after false-positive or incidental test results. Supplement with relevant data if differences can be expected for specific subgroups. Disease-specific mortality is a proportion of the all-cause mortality. It should be noted that even if a given treatment reduces one type of death, it could increase the risk of dying from another cause, to an equal or greater extent. Disease-specific mortality is typically presented as rates and as age- and risk- adjusted measures such as HR. It is a frequently used endpoint in screening trials, where it is considered to be subject to bias. Supplement with relevant data if differences can be expected for specific subgroups. Specific to diagnostic technologies: In diagnostic and screening technologies, this issue refers to the expected beneficial effect of the test-treatment chain. Specific to screening technologies: In diagnostic and screening technologies, this issue refers to the expected beneficial effect of the test-treatment chain. With screening tests, one should consider the effects of lead-time bias, length-time bias and selection bias to the mortality.		

AE	Topic	Issue	Clarification	Importance **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening.	
				Mandatory	Non-mandatory
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	Report the results both in absolute terms and relative to the comparator. Describe the efficacy and effectiveness of the technology on relevant disease outcomes (symptoms and findings). Outcomes such as function, QoL and patient satisfaction are reported in other assessment elements of this domain. Report changes in severity, frequency and recurrence of symptoms and findings. Supplement with relevant data if differences can be expected for specific subgroups. (See guideline on _Endpoints used for REA of pharmaceuticals – Clinical endpoints_).	M P S	(D = Not applicable)
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Report the results both in absolute terms and relative to the comparator. Report here efficacy and effectiveness outcomes such as complete cure, progression-free survival, time-to-event, next stage of disease, relapse. Describe here the duration of treatment effect on symptoms and findings: permanent, short-term, long-term, intermittent, undulating. Supplement with relevant data if differences can be expected for specific subgroups.	M P S	(D = Not applicable)
D0011	Function	What is the effect of the technology on patients' body functions?	Report the results both in absolute terms and relative to the comparator. International classification of function proposes the following categories for body functions: mental, sensory and pain, voice and speech, cardiac, respiratory and immune functions, genitourinary and reproductive functions, movement-related, and skin functions. Report the results both in absolute terms and relative to the comparator. Supplement with relevant data if differences can be expected for specific subgroups.	M P S D	–

AE	Topic	Issue	Clarification	Importance **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening.	
				Mandatory	Non-mandatory
D0016	Function	How does the use of the technology affect activities of daily living?	Report the results both in absolute terms and relative to the comparator. Supplement with relevant data if differences can be expected for specific subgroups. Activities of Daily Living (ADL) is used in rehabilitation as an umbrella term relating to self-care, comprising those activities or tasks that people undertake routinely in their everyday life. The activities can be subdivided into personal care and domestic and community activities.	–	M P S D
D0012	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Report the results both in absolute terms and relative to the comparator. Supplement with relevant data if differences can be expected for specific subgroups. Health related quality of life (HRQoL) is typically measured with self- or interviewer-administered questionnaires to measure cross-sectional differences in QoL between patients at a point in time (discriminative instruments) or longitudinal changes in HRQoL within patients during a period of time (evaluative instruments). Two basic approaches to HRQoL measurement are available: generic instruments that provide a summary of HRQoL; and specific instruments that focus on problems associated with single disease states, patient groups, or areas of function. Generic instruments include health profiles and instruments that generate health utilities. Each approach has its strengths and weaknesses and may be suitable for different circumstances.	M P S D	–

AE	Topic	Issue	Clarification	Importance **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening.	
				Mandatory	Non-mandatory
D0013	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Report the results both in absolute terms and relative to the comparator. Supplement with relevant data if differences can be expected for specific subgroups. HRQoL is typically measured with self- or interviewer-administered questionnaires to measure cross-sectional differences in QoL between patients at a point in time (discriminative instruments) or longitudinal changes in HRQoL within patients during a period of time (evaluative instruments). Two basic approaches to HRQoL measurement are available: generic instruments that provide a summary of HRQoL; and specific instruments that focus on problems associated with single disease states, patient groups, or areas of function. Generic instruments include health profiles and instruments that generate health utilities. Each approach has its strengths and weaknesses and may be suitable for different circumstances.	M P S D	–
D0017	Patient satisfaction	Were patients satisfied with the technology?	Describe patients' overall perception of the value of the intervention and their satisfaction with the treatment. For further information, see guideline on *Endpoints used for REA of pharmaceuticals – Clinical endpoints*.	–	M P S D
4. Safety					
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	Here, one should identify and describe the direct harms of the use and the administration of the technology and the comparator(s). Highlight the differences in the most important risks (i.e. the most severe and frequent harms) of the technology and its comparator and consider if there are uncertainties with regard to safety because of small numbers and/or short duration of follow-up.	M P S	–

AE	Topic	Issue	Clarification	Importance **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening.	
				Mandatory	Non-mandatory
			Consider: • What is the frequency and what are serious adverse events (SAEs) of the technology in relation to the comparator(s)? • What are the most frequent AEs of the technology in relation to the comparator(s)? • What is the frequency of discontinuation of treatment due to AEs of the technology in relation to the comparator(s)? • What is the frequency of SAEs leading to death for the technology in relation to the comparator(s)? • What is the frequency of unexpected AEs in participants and comparison groups?	D	
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	This is usually relevant with pharmaceuticals but may also be relevant with medical devices and procedures. Before marketing authorisation, it is relevant to report harms at any dose. After market access, the harms at doses normally used in practice are most relevant for HTAs. Information should be included if safe use of the technology is sensitive to even small changes of the dose because this may have implications for the training and organisation of care. The potential for accumulated harm due to repeated dosage or testing should also be considered. Specific to pharmaceuticals: For further information, see guideline on *Endpoints used for REA of pharmaceuticals – Safety*.	P	M S D
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	This issue is especially relevant for new or evolving technologies where there are considerable uncertainties in the safety evidence, and in technologies with steep learning curves. How does the safety profile of the technology vary between different generations, approved versions or products? Is there evidence that harms increase or decrease in different organisational settings?	M S D	P

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C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	Typically, people with comorbidities and co-medication, pregnancy, intolerances, specific genetic profiles, elderly people, children and immunosuppressed patients. Are there any relevant contraindications or interactions with other technologies?	M P S D	–
C0007	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	Describe here what is known of the harms caused by the properties or behaviour of professionals, patients or other individuals who apply or maintain the technology. Is there e.g. a noteworthy risk of malfunction of a device, due to deficient user training or personal attitude; or a risk of errors related to reconstitution, dosage, administration or storage of medicines, that may have serious consequences; or, is there a risk of addiction? Describe what is known of the learning curve, intra- or inter-observer variation in interpretation of outcomes, errors or other user-dependent concerns in the quality of care. For further information, see guideline on *Endpoint used for REA of pharmaceuticals – Safety*.	–	M P S D
B0010	Investments and tools required to use the technology	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?	Describe the data that needs to be collected about the care process, professionals involved, patients and their health outcomes. These include clinical indications, specified populations, prescriber information, inpatient or outpatient use, test results, review period and health outcomes. In case of new technologies, consult the EVIDENT database. Specific to pharmaceuticals: refer to the SPC and EPAR. Describe the general importance of having a registry to monitor the use of this particular technology and the comparator. Are there existing registries that should be used, or should a registry be established, to collect the necessary data to monitor safety or true life effectiveness? Provide national examples. Sometimes registries are connected with the risk-	M	P S D

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				Mandatory	Non-mandatory
			sharing scheme that innovative pharmaceuticals require in some countries. Notice also the requirements of pharmacovigilance monitoring.		

Further AEs for diagnostic and screening technologies only

AE	Topic	Issue	Clarification	Relevance	

AE	Topic	Issue	Clarification	Relevance	
D0032	Morbidity	How does the test-treatment intervention modify the magnitude and frequency of morbidity?	A more accurate replacement test could improve treatment and effectiveness. A satisfactory triage test may decrease the number of adverse outcomes from another test. An add-on test may increase sensitivity so that more patients receive proper treatment and thus improved outcomes.	D	(S=not applicable)
D1001	Test accuracy	What is the accuracy of the test against reference standard?	Accuracy in terms of sensitivity and specificity, and other measures such as likelihood ratios, pre-test probabilities, SDORs, area under the curve (AUC) or Q*.	D S	-
D1005	Test accuracy	What is the optimal threshold value in this context?	Sensitivity and specificity vary according to the threshold value. Optimal combination of sensitivity and specificity defines optimal threshold value. The optimum depends on the consequences of the test results, e.g. whether it does more harm to overlook a case or to treat someone unnecessarily. Specific to screening technologies: In screening programmes, one should consider separately the screening test and the subsequent diagnostic tests.	D S	-
C0006	Patient safety	What are the consequences of false-positive, false-negative and incidental findings generated by using the technology from the viewpoint of patient safety?	What are the consequences of false-positive, false-negative and incidental findings generated by using the technology? False-negative test results (Type II error) identify sick people incorrectly as healthy with the possible consequence of incorrectly rejected or delayed treatment. The volume of false-negative test results can be estimated to be 1-sensitivity of the test. False-positive test results (Type I error) identify healthy people incorrectly as sick with the possible consequence of over-treatment. The volume of false-positive test results can be estimated to be 1-specificity of the test. Incidental findings in tests carry major risk of over-diagnosis and over-treatment. Specific to screening technologies : In screening programmes, one should consider separately the false-negative screening test	D S	-

AE	Topic	Issue	Clarification	Relevance	
			results and the subsequent false-negative diagnostic test results.		