Joint Action on HTA 2012-2015

Procedure Manual for Rapid REAs of other technologies

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

WP Co-Lead Partner: LBI HTA

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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Joint Action on HTA 2 (2012-2015)

PROCEDURE MANUAL WP5 STRAND B: RAPID RELATIVE EFFECTIVENESS ASSESSMENT OF OTHER HEALTH TECHNOLOGIES SUCH AS MEDICAL DEVICES, SURGICAL INTERVENTIONS OR DIAGNOSTICS

Version log

Version number	Date	Name (Initials)	Comment
V1	20/12/2012	AN	V1 was sent to WP5 members for comments (consultation period: 20 Dec 2012 – 21 Jan 2013)
V2	15/03/2013	AN	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	29/04/2013	AN	Comments from the WP5 SAG were processed and alterations based on these comments were incorporated
V4	20/11/2015	AN, JM	Based on the experiences gained and on the comments received from pilot rapid assessment producers in WP5B, this Procedure Manual was updated.

Coordination Team

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Acronyms – Abbreviations

A	(in the project phase titles) stands for Assessment
C	(in the project phase titles) stands for Consultation
CT	Coordination team
E	(in the project phase titles) stands for Evaluation
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment
JA	Joint Action
JA2	Joint Action 2
P	(in the project phase titles) stands for Project Planning (Protocol)
PICO	Abbreviation used for scoping: P=population, I=intervention, C=comparison, O=outcome
POP	Planned and On-going Projects
R	(in the project phase titles) stands for Review
REA	Relative effectiveness assessment
SAG	Stakeholder Advisory Group
SF	Stakeholder Forum
T	(in the project phase titles) stands for Topic selection and Team building
WP	Work Package

1. Introduction

1.1 Objective of this Procedure Manual

This Procedure Manual guides the production of rapid assessments of other health technologies such as medical devices, surgical interventions or diagnostics in Work Package 5 (WP5) Strand B.

1.2 Background information on Work Package 5 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 WP5 of EUnetHTA JA2 are to

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

2) test the application (translation) of those collaboratively produced HTAs in national/local contexts.

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

ad 1) Testing and piloting collaborative production

6 pilot rapid assessments on other technologies such as medical devices, surgical interventions or diagnostics containing rapid HTA information based on structured core information from the HTA Core Model® for Rapid Relative Effectiveness (REA) were collaboratively produced. The experiences gained have been used for informing this Procedure Manual.

ad 2) Transferring rapid HTA or parts of the information into national/local reports

All WP5 members were expected to put an effort into the adaptation of rapid assessments produced within WP5 into national/local reports. This may take different forms: e.g., either the whole rapid assessment can be used as a local report when referenced accordingly, or only parts of the assessment can be used for national/local reports (e.g., conclusions/discussion are reformulated). For each rapid assessment, 2 national/local reports should be produced using information of the assessments. Information on the current level of uptake can be found here: http://www.eunethta.eu/national-uptake .

ad 3) Development and testing of models and tools as well as production processes to support collaborative and national production

During the joint production of rapid assessments, the following products have been tested and were further developed based on the experience gained:

- the “HTA Core Model® for Rapid REA”
- templates for calls for collaboration, Project Plans, rapid assessments
- the “Submission file template” developed by WP7 Subgroup 4.

1.3 Objectives of pilot rapid assessments

The purpose of pilot rapid assessments was to produce assessments based on cross-border collaboration and to test the usability of the “HTA Core Model® for rapid REA” including guidelines for other technologies. Relevant outcomes of the pilot rapid assessments are:

- pilot teams’ perception about the cross- border collaboration in producing a rapid assessment
- WP5 members’ perception on the usability/readability of the rapid assessment

- the duration of the assessment
- the workload (in terms of working hours)
- assessment teams' perception on the applicability of the "HTA Core Model® for rapid REAs" and the guidelines to other technologies
- transferability of the assessments to the national/ local context.

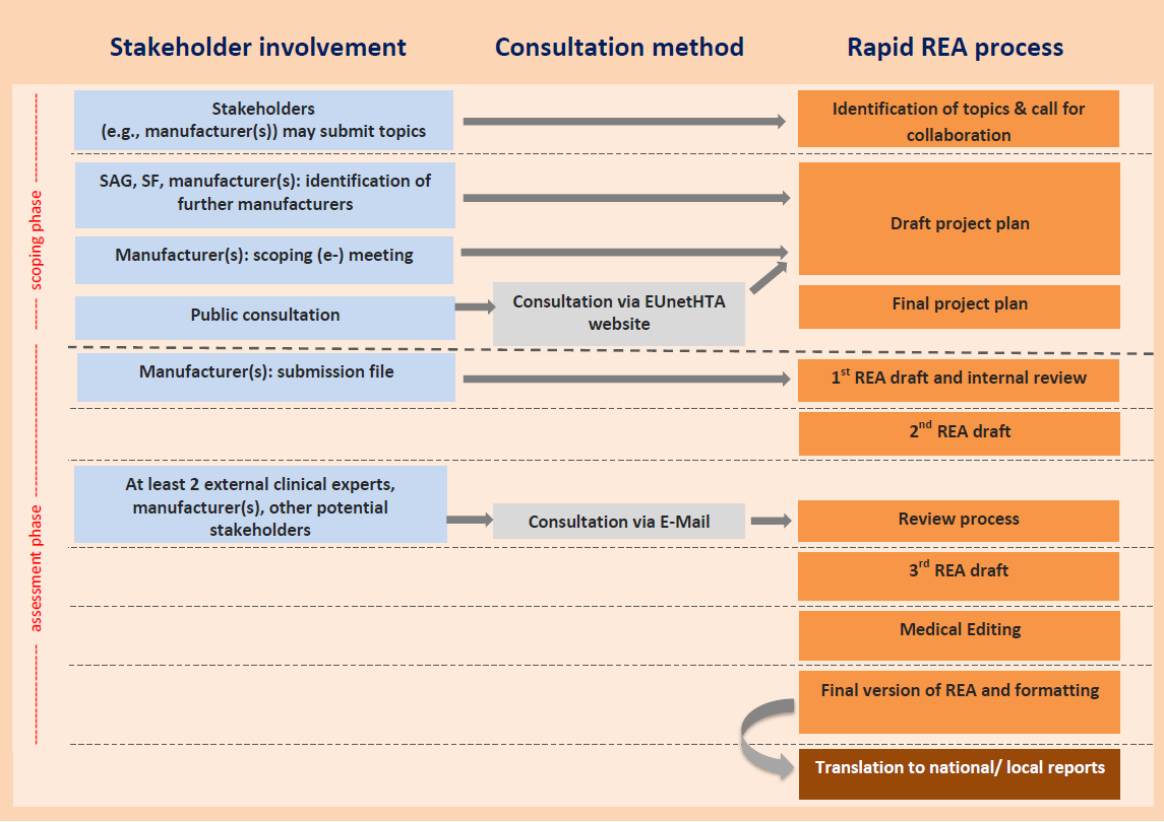
2. Project management

2.1 Process of rapid assessments

A schematic overview of the organisation of the process of the rapid assessments is included in

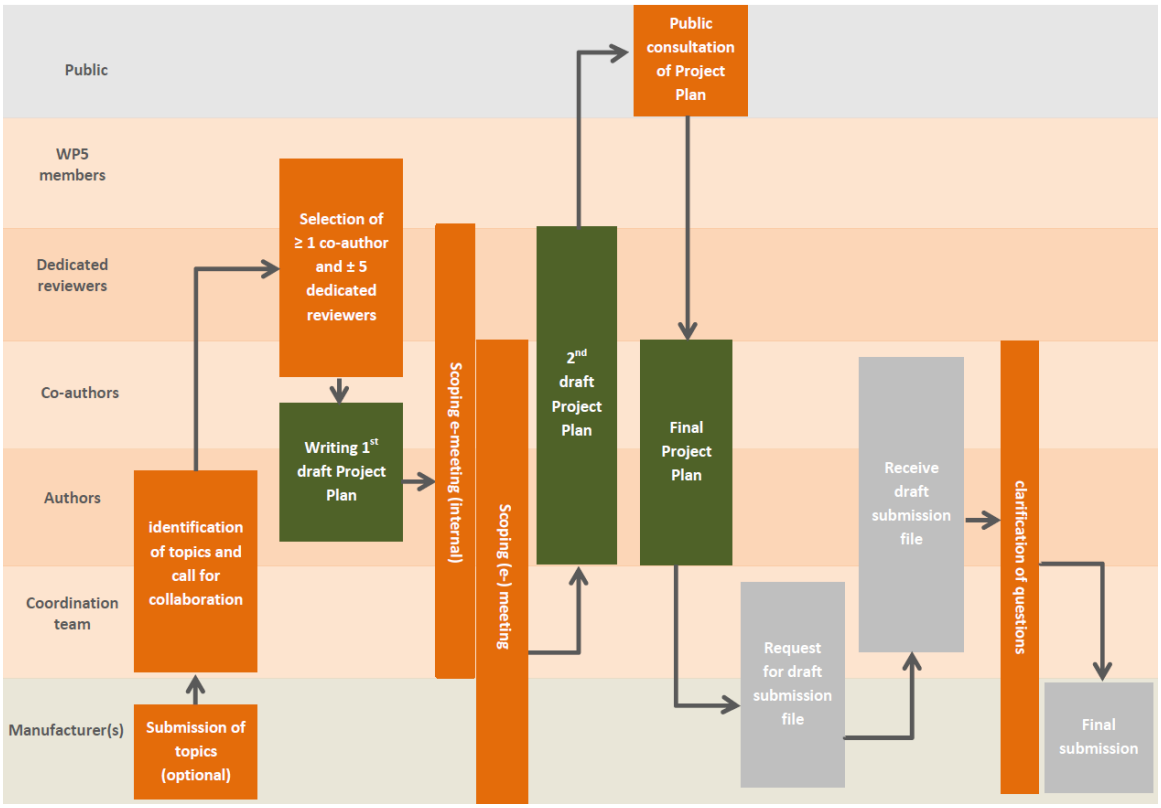
Figure 1 (overview on stakeholder involvement), Figure 2 (scoping phase) and Figure 3 (assessment phase). These overviews should be read as an ideal picture due to the high possibility of divergence (e.g., deviations from timelines). The different steps and their timing are presented in Table 1 and Table 2.

Figure 1: Overview on stakeholder involvement



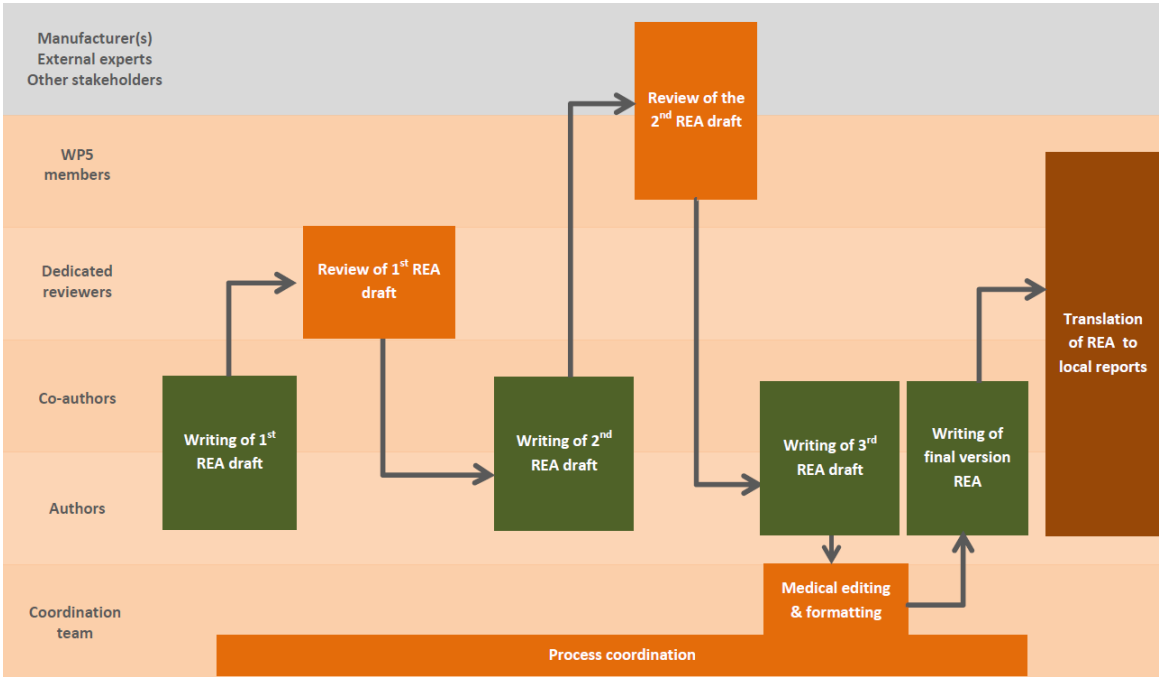
Abbreviations: REA - Relative Effectiveness Assessment; SAG - Stakeholder Advisory Group; SF - Stakeholder Forum

Figure 2: Overview Scoping Phase



Abbreviations: WP - Work Package

Figure 3: Overview Assessment Phase



Abbreviations: REA - Relative Effectiveness Assessment; WP - Work Package

Table 1. Proposed schedule of rapid assessments - Scoping phase

Project Planning/ Scoping Phase				
Start [working days]	**End [working days]**	**Activity**	**Target group**	**Parties involved**
-	+10	Topic identification: • Call for collaboration • Identification of topics via POP database	Strand B members	Authoring agencies, CT
-	-	Identification of manufacturer(s)	Authors, co-authors	Authors, co-authors, dedicated reviewers, Strand B members, SAG, SF, manufacturer(s), CT
-	-	Scoping and development of draft Project Plan	Dedicated reviewers	Authors, co-authors, external experts, patients
-	-	Internal scoping e-meeting	Manufacturer(s)	Authors, co-authors, dedicated reviewers, CT
-	-	Scoping (e-)meeting with manufacturer(s)	Dedicated reviewers, external experts, patients	Manufacturer(s), authors, co-authors, CT
	+5	Consultation of draft Project Plan with dedicated reviewers	Authors, co-authors	Dedicated reviewers
	+5	Amendment of draft Project Plan	WP5 SAG, SF, manufacturer(s), Public	Authors, co-authors
-	+15	Public consultation of draft Project Plan	Authors, co-authors, dedicated reviewers	WP5 SAG, SF, manufacturer(s), Public
-	+10	Publication of final Project Plan and comments including assessment team's answers	Public	Authors, Co-Authors, dedicated reviewers, external experts, patients, CT
-	-	Send request for draft Submission file template to manufacturer(s)	Manufacturer(s)	CT, authors, co-authors
-	approx. +30	Completion of Submission file template by manufacturer(s)	Authors, co-authors	Manufacturer(s)
	+ 10	Clarifying further questions concerning draft Submission file	Manufacturer(s)	Authors, co-authors
-	+ 10	Final Submission file	Authors, co-authors, dedicated reviewers	Manufacturer(s)

Abbreviations: CT = coordination team; SAG = Stakeholder Advisory Group; SF = Stakeholder Forum

Table 2. Proposed schedule of rapid assessments - Assessment phase

Rapid assessment phase				
Start [working days]	**End [working days]**	**Activity**	**Target group**	**Parties involved**
0	35	Writing first draft rapid assessment	Dedicated reviewers	Authors, co-authors
35	45	Review by pool of ± 5 dedicated reviewers	Authors, co-authors	Dedicated reviewers
45	60	Writing second draft rapid assessment	Strand B members, at least 2 clinical experts, manufacturer(s), other potential stakeholders	Authors, co-authors
60	75	Review by ≥ 2 external clinical experts, WP5 Strand B members, manufacturer(s) and by other potential stakeholders	Authors, co-authors	Strand B members, at least 2 clinical experts, manufacturer(s), other potential stakeholders
75	90	Writing third draft rapid assessment	CT, medical editor	Authors, co-authors
90	100	Medical Editing	Authors, co-authors	Medical editor, (CT)
100	110	Writing of final version of rapid assessment	CT	Authors, Co-Authors
110	115	Formatting	CT	Graphic designer
115	120	Final version of REA	Public	CT
120	-	Translation of rapid assessment to national/local reports	National HTA organisations or institutions	WP5 members, members from other WPs

2.2 Rapid assessment team

Every team involved in the production of a rapid assessment will be composed of:

- first author(s): from 1 authoring organisation or institution
- (co-)author(s): from ≥1 co-authoring organisation or institution
- a pool of dedicated reviewers: from 2 – 5 reviewing organisations or institutions
- ≥ 2 external medical experts
- Coordination Team (CT)
- whenever possible, patient representatives should also be involved.

For the production of rapid assessments, the authoring of the 4 domains is limited to a few authors. To ensure broad participation and quality assurance, several organisations are involved in the in-depth review of the assessment as dedciated reviewers. If appropriate and feasible other collaboration models may be applied during production of the rapid assessments.

Specific roles and tasks of team members are described below.

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

Authors are responsible for the overall quality of the final assessment, the adherence to deadlines and its timely completion. They are responsible for facilitating and overseeing the joint production and for the adherence to EUnetHTA Guidelines.

As soon as the topic has been decided on, 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 according to the template of the Project Plan. They are also responsible for identifying ongoing trials and take their finalisation dates into account when planning the timelines for the assessment. They also decide at this stage how the tasks within the assessment team (i.e. the sharing of the workload) will be distributed.

During the scoping process authors play an active role in arranging scoping e-meetings with the assessment team. Whenever deemed feasible, authors are also responsible for preparing and managing scoping (e-) meetings with the manufacturer(s) to inform the Project Plan for public consultation. Authors, together with co-authors, take into consideration all comments received on the draft Project Plan including comments received via public consultation. In cooperation with the co-authors, they are responsible for producing a final Project Plan and to provide answers to all comments received during public consultation within 10 days after the end of the public consultation.

After the final Project Plan has been produced, authors and co-authors can use the Submission file for medical devices to ask manufacturer(s) for specific information on the respective technology. Authors and co-authors then select relevant items from the Submission file template for medical devices which manufacturer(s) should fill in. Based on the first draft Submission file, they have to formulate any open questions within 10 working days which are then sent for clarification to the manufacturer(s).

They lead the production of the first draft of the rapid assessment and they produce the summary section of the assessment integrating information from all domains. They take into consideration and answer the dedicated reviewers' comments and suggestions, and produce together with the co-authors the second version of the rapid assessment. They consult the second draft of the rapid assessment with external reviewer(s), manufacturer(s) and Strand B members. They are responsible for answering/incorporating comments which apply to their domains and ensure that all comments have been addressed appropriately.

Authors are responsible for integrating comments received from medical editors and for the timely publication of the rapid assessment alongside comments and answers received on the different versions of the rapid assessment.

After finalisation of the rapid assessment, whenever possible, first authors should use the rapid assessment for their own national/local REA.

In case of any disagreements within the assessment team (i.e. with co-authors and/or dedicated reviewers or the CT), authors have the final decisional power and are responsible for any decisions made. Also, authors are responsible for a transparent way of dealing with any disagreements within the assessment team.

2) **Co-author(s)** – play a supportive role during the scoping phase and take active part in the production of the rapid assessments.

During the scoping phase co-authors contribute to drafting the Project Plan and they actively participate in scoping e-meetings. They agree on the selection and formulation of research questions, on all items of the PICO question, the planned extraction tables and the methodology. Co-authors contribute to incorporating comments received on the draft Project Plan, they accept the final Project Plan and agree on timelines proposed.

Co-authors support first authors in selecting relevant items from the Submission file template, and they are involved in the scoping (e-) meeting with the manufacturer(s). Co-authors review and provide input to the draft Submission file and assist authors in defining clarifying questions.

Co-authors take an active part in the production of rapid assessments. They verify the content produced by the first authors, the studies included, the risk of bias tables and data extraction and they agree with the conclusion(s) derived in the assessment. Together with first authors, they consider comments and suggestions for changes collected from dedicated reviewers, WP5 members, external experts, manufacturer(s) and patients.

After finalisation of the rapid assessment, whenever possible, co-authors should use the rapid assessment for their own national/local REA.

Model(s) for collaboration of first authors and co-authors

Even though there is a close cooperation between first authors and co-author(s) during the production of the rapid assessment, the roles of the first author and co-author(s) should be flexible enough so as they can cooperate in the most convenient and efficient way. It is suggested that decisions about the division of work are made at the very beginning of the assessment and to 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 2 suggested ways of the division of tasks and responsibilities:

a) First authors will be responsible for the production of all domains, including data extraction from clinical trials, finding answers to the questions listed in the Project Plan and writing the assessment, whereas co-authors will follow and verify every step taken by the first author during the production of the assessment, including data extraction, verification of references, risk of bias tables and adherence to methods. In case of persistent disagreement between authors, dedicated reviewers can also serve as consultants, but the final decisional power rests with the first authors. If there is a strong divergence of opinions between producers, the reason (e.g. weak evidence, heterogeneity of findings, differences in interpretation) will be included in the Discussion section of the rapid assessment.

b) Workload in the production of the domains can be divided between author and co-author(s). Then, it is highly suggested that the first author produces both the Clinical Effectiveness and the Safety domain and that co-author(s) compile the other two domains. Production of domain reports includes data extraction from clinical trials, finding answers to the questions listed in the Project Plan and finally, writing the domain report. The content produced by first authors will be verified by co-authors and vice versa. The first author has to oversee the whole process and has to merge all parts of the Project Plan and the assessment into one document and they have to produce the Summary section of the rapid assessment.

There might be several other ways of dividing tasks and responsibilities and if appropriate and feasible, other collaboration models can be used in the production of the assessments.

3) **Dedicated Reviewers** – play a supportive role in both phases of the project: scoping and production of rapid assessments.

Reviewers are encouraged to support authors from the very beginning of the project. They will participate in the scoping e-meeting and they review the draft Project Plan. They agree on the chosen intervention, population or any restrictions to the population, the endpoints and comparators. Dedicated reviewers make sure that the Project Plan is in alliance with current EUnetHTA guidelines. They accept the Project Plan and agree on timelines.

In cases of disagreement between first author(s) and co-author(s), dedicated reviewers will be consulted and will actively provide their input. Whenever needed, reviewers will serve as consultants for authors.

Reviewers' major task is to make a review and verify the first version of the rapid assessment and to send comments and suggested changes to authors. As their main role in the process is to ensure the quality of the rapid assessment, dedicated reviewers are requested to review the draft assessment thoroughly, taking into account the studies selected by the authors (appropriate inclusion of studies, checking the sources of information, checking data extraction tables), cross-checking results (risk of bias tables, grading of the body of evidence) and conclusions (scientific soundness of the analyses performed), and the adherence to EUnetHTA guidelines. All suggestions of the reviewers have to be considered by the authors. If authors decide to reject the proposed changes, it must be reliably justified and documented (e.g. in the table of comments).

After finalisation of the rapid assessment, whenever possible, reviewers may use it for the production of their own national/local REA.

4) **Coordinating team** – coordinates the work within the rapid assessments and between rapid assessments.

The CT facilitates the identification of topics using the POP database, they assist in building the assessment team and in identifying topics by sending out and by managing calls for collaborations. They collect the Declaration of Interest and Confidentiality Undertaking (DOICU) forms of all assessment team members and share them with the secretariat. They set up the Intranet group for the assessment and they are responsible for uploading all necessary templates for compiling the assessment.

They support and they are involved in any communication within the assessment team and they are the main point of contact for external stakeholders (e.g., manufacturer(s), Stakeholder Advisory Group (SAG)). The CT supports the assessment team whenever needed in identifying manufacturer(s), external experts and patient representatives. The CT assists authors in organising e-meetings and scoping (e-)meetings. They send the draft Submission file template and the draft assessment to manufacturer(s) and collect and process all answers received. They manage the final steps of the assessment phase by identifying medical editors and by formatting the final rapid assessment. They publish the final assessment on the EUnetHTA Homepage in collaboration with the Secretariat.

5) **External medical experts**: inform the scope of the assessment, answer specific questions of the assessment team and comment on the second draft of the assessment to ensure its clinical correctness.

At least two external experts should participate in the assessment; ideally one expert on the technology and one expert in the disease area (suggestions of the SAG should be taken into account and only one expert should be chosen by the authors). Identification of external experts should be done in due time to allow delays. European associations and/or members of relevant guideline panels can be contacted.

External experts have to sign a DOICU form which will be collected at the beginning of the assessment and prior to any involvement in the rapid assessment. External experts who declare a conflict of interest according to the current EUnetHTA Procedure Guidelines for handling Declaration of Interest and Confidentiality Undertaking will be excluded from parts of or the whole work under the specific topic. However, they still may be included in work of other rapid assessments.

If needed, other experts (e.g. statisticians) may be invited as external reviewers.

2.3 Working instructions for authors of rapid assessments

Basic documents/tools for the assessment teams are:

- This Procedure Manual
- HTA Core Model® for Rapid REA (see HTA Core Model for Rapid REA)
- The Guidelines on methodological issues (Guidelines) produced within JA1 and JA2
- Assessment elements from other HTA Core Model Applications
- Templates for the Project Plan and rapid assessments
- Whenever possible, the HTA Core Model® Online Tool will be used for the rapid assessments

- Submission file template for medical devices

The instructions in this Procedure Manual divide the tasks into 6 main phases: **topic selection and team building, project planning, assessment, internal review, external review and consultation, and evaluation**. These phases are further divided into numbered sections.

- **Phase 1: Topic selection and team building** (marked with T) includes the identification of the topic (call for collaboration or POP database) and the compilation of the assessment team, including first authors, co-authors and dedicated reviewers. Also, the roles within the team are defined. The objective of this phase is to build an operational team for a topic considered relevant by EUnetHTA members.

- **Phase 2: Project planning** (marked with P) includes scoping, searching of information, formulating research questions, and planning of methodologies. In addition, this phase includes the identification and the initiation of contacts with stakeholders. 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 to be used in the assessment.

- **Phase 3: Assessment** (marked with A) includes finding answers to the questions specified in the project planning phase based on guidance contained in the HTA Core Model® for rapid REA and the methodological guidelines. The objective of this phase is to compile a first draft assessment.

- **Phase 4: Internal Review** (marked with R) includes a first internal review of the assessment. The objective of this phase is to collect and address comments and suggestions for changes from dedicated reviewers and to produce a second draft of the assessment.

- **Phase 5: External Review and Consultation** (marked with C) includes consultation of the assessment with WP5 members, at least 2 clinical experts, the manufacturer(s) and other potential stakeholders (e.g. patients, payers). Based on the comments and opinions from all parties a third draft of the assessment is produced. The overall objective of this phase is to produce the fourth version and thus the final assessment which is ready for publication after medical editing and formatting.

- **Phase 6: Evaluation phase** (marked with E) includes the evaluation of lessons learned by collecting information and opinions from assessment team members, other WP members and - if applicable - other parties such as manufacturer(s) through a range of standardised surveys. The objective of this phase is to gather recommendations for continuously improving processes.

2.4 Communication

Internal communication

Managing the draft

The authors work mostly in text documents. They should clearly mark changes they make in the draft assessment; either using the track changes option or using different colours or fonts. Only the authors of the respective domains have the right to accept or reject the changes, to form a new draft or to complete the assessment. Reviewers should provide their comments through the standardised comments table. To avoid confusion, authors and co-authors should only work with one current version of the document, not producing various different versions.

The teams can decide whether they circulate the drafts as e-mail attachments or use the EUnetHTA Intranet group. For each of the rapid assessments, an own Intranet group will be generated, including all members of the respective assessment team. Authors are highly encouraged to use the Intranet group for discussions and for sharing documents with the assessment team members.

The HTA Core Model® Online (access at http://meka.thl.fi/htacore/Default.aspx) can also be used and guides authors through the individual research questions which have to be considered when conducting rapid assessments. Once the scope is set, the assessment template can be downloaded. When the final assessment is ready it can be uploaded into the HTA Core Model® Online. To log in to the Online Tool, you need to have a EUnetHTA ID. If your organisation is a EUnetHTA Partner or Associate, you can get a EUnetHTA ID by contacting the EUnetHTA Secretariat.

EUnetHTA Intranet groups

Relevant documents (e.g., templates, meeting minutes, reports) will be stored at the WP's EUnetHTA Intranet site. The CT and the authors are responsible for uploading relevant documents to the groups.

You can access the Intranet site by clicking the "Access our Intranet" in the bottom left corner of the EUnetHTA public webpage http://www.eunethta.eu/ or directly by entering https://intranet.eunethta.eu. There you should have direct access to the 'Rapid HTA' group (listed under "My groups" on the right). There is a guide for the use of the EUnetHTA Intranet site: https://intranet.eunethta.eu/system/files/eunethta_intranet_user_manual_1.6.pdf. If you do not have the username and password to enter, please contact the EUnetHTA Secretariat.

Brief guidance to the Document Library on the Intranet:

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.

E-meetings

There is an e-meeting facility, Saba centra, available for EUnetHTA projects. The CT will set up e-meetings and send the invitations to the participants if required. Assessment teams may also use Saba centra to facilitate their own internal meetings. However, only Associated Partners can set up an e-meeting, with up to 15 participants. All partners can participate.

E-meetings with all assessment members are highly recommended to discuss the draft Project Plan, to agree on methods, research questions, timelines, the PICO question and on the division of tasks amongst authoring agencies. Authors are encouraged to schedule one e-meeting at the beginning of the scoping phase at least.

At the Intranet site you can find a pdf-guide for Saba Centra https://intranet.eunethta.eu/system/files/saba_centra_7-6_essentials_guide.pdf .

External communication

All external communication will be handled by the CT.

The draft Project Plan is available for public consultation on the EUnetHTA website. The SAG, the Stakeholder Forum (SF) and the manufacturer(s) have to be notified by the CT about the opportunity to comment on the draft Project Plan. The final Project Plan, all comments received and answers provided by the authors have to be made publicly available on the EUnetHTA Homepage within 10 working days.

There will be a consultation of the rapid assessment with WP5 members, external experts, the manufacturer(s) and - if applicable - other relevant stakeholders like patient representatives, but there will be no public consultation to seek further feedback on the assessment.

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

3. Assessment stages

3.1 T - Topic selection and team building

Selection of topics and identification of collaborating partners includes 2 potential ways:

a) Model 1: “Call for collaboration“ (active brokering) to find partners:
Authoring organisations or institutions have identified relevant topics out of their own work-programs. Authors should suggest at least 2 topics inclduing a rationale why these topics have been chosen. These suggestions as well as suggested time-frames (chapter 5.1 Call for Collaboration Form) are submitted to the CT. The CT will send out the “Call for collaboration Form” asking Strand B members to prioritise these topics. The topic considered relevant by the majority of members is then selected for an assessment. Also, in the call for collaboration members are asked to indicate if they are interested in actively participating in the rapid assessment and to clarify which role they want to have, i.e. co-author or dedicated reviewer.

b) Model 2: Individually contacting partners with similar work programs based on the “Planned and Ongoing Projects” (POP) database:
Topics for collaboration could be identified via the POP database either by Strand members or by the CT or based on spontaneous reactions to POP-alerts on similar work-programs between several agencies. When there is an overlap in topics listed, authoring organisations may contact the respective organisation(s) themselves or they may ask the CT for assistance.

Generally, the topic should be procedure-specific and not technology-specific. When only one selected technology from a single manufacturer will be assessed, a good rationale for this choice has to be provided by authoring agencies. Only technologies with a CE mark for the indication qualify for assessments.

Other forms of topic selection can include the submission of topics by external parties. These topics will be distributed by the CT amongst authoring organisations asking them for expressions of interest in compiling a rapid assessment on the proposed topic.

Regardless of the method of topic selection, no additional workload should be imposed on participating organisations or institutions, since topics should be relevant for the work programs of the respective organisations or institutions.

3.2 P1 – Project planning

At the very beginning of the project planning phase, the **scope** of the project should be discussed and clearly defined. The guiding documents for this task are the EUnetHTA guidelines.

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

- **P**opulation / patients with the disease of interest
- **I**ntervention(s), i.e. the technology/-ies under assessment (assessments of other technologies should only include products with a CE mark)
- **C**omparison(s), that should serve as reference
- **O**utcomes which encompass the endpoints for assessing effectiveness and safety.

Template to be used: Table 3 (Project Scope and Objectives) of the Project Plan template. For other relevant considerations regarding the PICO elements see the HTA Model for Rapid Relative Effectiveness Assessment (section 2.1.).

The PICO will drive the evaluation in all domains. Population, intervention and comparison will generally be the same for all domains. However, there may be sometimes the need to deviate from the scope due to e.g. a subpopulation of special interest or a lack in data of the population defined in the scope. Scoping should be a subject for discussion with dedicated reviewers, external experts and, whenever possible, other stakeholders. A scoping e-meeting with all members of the assessment team is highly recommended. In addition, a (face-to-face or e-) scoping meeting between authors/CT and the manufacturer(s) is a valuable information source (see section P4).

3.3 P2 - Selecting relevant research questions

This phase involves:

- Selection of relevant research questions:
    - Selecting relevant issues from the assessment element table of the HTA Core Model® for rapid REA (see Appendix 5.2 Assessment element tables).
    - Going through the Checklist for potential ethical, organisational, patient and social and legal aspects of the HTA Core Model for rapid REA.
    - Selecting further relevant assessment elements of other HTA Core Model® Applications.
- Translating the selected issues (generic questions) into actual research questions (answerable questions).

Selecting relevant issues from HTA Core Models

The most important output of this phase is to retrieve a set of pragmatic and answerable questions for the assessment team to continue with.

The authors go through the generic questions, i.e. issues, in the assessment element table of every domain in the HTA Core Model® for rapid REA. The team goes through these issues, one by one, defining whether the question is relevant for this topic. If deemed relevant, if time allows, and to avoid missing other relevant aspects, issues of all domains of other applications of the HTA Core Model® (which can be found here: http://meka.thl.fi/htacore/BrowseModel.aspx) should be considered. Which issues are selected will eventually be based on the authors' own expertise, the literature retrieved, the timelines and possibly consultations with experts.

For usage within EUnetHTA, assessment elements from the HTA Core Model for rapid REA are labelled as 'mandatory' or 'non-mandatory' (see Appendix 5.2 Assessment element tables). 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 a justification. 'Non-mandatory' assessment elements can be included in the assessment, based on the experiences and preferences of authoring agencies; if authors choose to exclude these elements, they do not need to be provide a justification.

Formulating research questions

In this phase authors should translate the issues, i.e. the generic questions in the relevant assessment element table, into actual research questions. One issue usually translates into one actual research question, but sometimes there is a need to translate the single issue into 2 or more actual research questions. The word 'research question' is probably not always appropriate, as not all questions require scientific research (e.g. systematic review) in order to be answered. The answer may also be retrieved from a suitable registry or by expert consultation.

Examples from the pilot assessment on endovascular therapies using mechanical thrombectomy devices for acute ischaemic stroke:

In the Effectiveness domain the issue *"How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?"* was translated into a research question *"How does mechanical thrombectomy impact the symptoms and severity of acute ischaemic stroke?"*.

An issue in the Health problem and current use of technology domain *"What are the known risk factors for the disease or health condition?"* was translated into the research question *"What are the known risk factors for developing an acute ischaemic stroke?"*.

Template to be used: Table 5 (Assessment elements and translating research questions) of the Project Plan template, section 4.0.

3.4 P3 - Plan for methodologies of rapid 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 HTA Model for rapid REA, in the HTA Core Model and the Guidelines are the guiding documents for this task. Deviations have to be justified.

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 the Project Plan, this needs to be reported where indicated in the assessment template.

Not all research questions require a thorough systematic review, and in some research areas there are no established quality assessment criteria for information. This should also be reported for transparency. Authors can complement the basic search by a domain specific search. Sometimes, single research questions may require additional tailored searches.

The following issues should be reported:

- Plan for information retrieval: sources and search terms for locating domain specific information, inclusion/exclusion criteria for studies or other information, in terms of content, methods and quality.
- Plan for handling published data: do a systematic review, cite recent reviews, “screen until saturated” etc.
- Plan for finding information when there is no published data: From web sites of organisations, discussion forums, registers, conducting a survey (questionnaire, interview), other type of own research (analysis of primary data, modelling etc).
- Quality assessment tools or criteria planned to be used.
- Plan for synthesis: evidence table, plan for meta-analysis or qualitative synthesis, use of GRADE, etc.

Template to be used: Table 4a (Project approach and method) and Table 4b (Preliminary evidence) of the Project Plan template, section 4.0.

Note that for technologies other than pharmaceuticals, available evidence will depend on the stage of a technology within its product life cycle, i.e. emerging or established, and also on the type of technology, e.g. technologies indicated for diagnostic or screening purposes in comparison to therapeutic interventions.

3.5 P4 - Scoping (e-) meeting with manufacturer(s)

The authors and co-authors, together with the CT, discuss the possibility of a scoping (e-)meeting at the beginning of the scoping phase. Whenever feasible, it is recommended to organise a face-to-face or e-meeting with authors, co-authors, manufacturer(s) and, if deemed necessary, representatives of the CT.

The objective of such a meeting is to discuss the scope of the assessment and to gain information on the devices included (e.g., technical characteristics and mode of operation), relevant comparators, patient groups and outcomes. Thus, these meetings are considered as a valuable source for defining the final scope. Information gained from the scoping meeting is then considered for developing the final Project Plan. However, only after public consultation the final is Project Plan ready.

3.6 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 Project Plan. This draft will be subject of a public consultation on the EUnetHTA website for a period of 15 working days. Members of the WP5 SAG, the SF and WP5 Strand B members will be notified about the opportunity to provide comments. Comments received will have to be taken into account by the authors prior to the compilation of the final Project Plan. The authors are responsible for answering all comments received in a standardised form.

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 CT).

3.7 P6 - The Submission file template

The Submission file template for medical devices developed by WP7 Subgroup 4 summarises scientific requirements for reimbursement across Europe. Already at the beginning of the scoping phase, the authors and co-authors, together with the Coordination Team (CT), decide about the usage of the Submission file template for the respective assessment. The final decision on the usage of the Submission file is made by the authors. In case the Submission file is used, manufacturer(s) of the chosen intervention are informed by the CT about the possibility to submit relevant information on their device via this standardised form. It is, therefore, recommended to allow enough time for identifying all relevant manufacturer(s) and to establish personal contacts. In addition, manufacturer(s) have to be notified about the Submission file well in advance to allow internal planning for submitting the information requested (at least 30 days, ideally 50 days prior to the submission).

To receive relevant information from the manufacturer(s), the authors indicate which parts of the Submission file template are relevant for the rapid assessment and need to be filled in. Therefore, the authors and co-authors, possibly together with dedicated reviewers and external experts, select relevant modules from the Submission file template. Based on experiences within JA2 assessments, it is suggested to focus on the first two domains (TEC and CUR) when selecting the modules.

After the final Project Plan is available, the draft Submission file template is sent to the manufacturer(s) for completion for a period of approx. 30 working days.

The Submission file is evaluated by the authoring agencies for its completeness. The evaluation of the Submission file should focus on several critical issues:

- Completeness of information provided.
- If applicable, 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.
- If applicable, the risk of bias should be assessed independently by the assessment team and information provided in the Submission file should be appraised critically.
- If applicable, the inclusion and exclusion criteria for the literature selection provided in the Submission file should be re-evaluated for their appropriateness.

After the Submission file has been evaluated, the authors and co-authors have the possibility to formulate clarifying questions or ask for additional information within 10 working days. Manufacturer(s) should then provide this further information within 10 working days.

3.8 A1- Assessment phase

In this phase authors have their Project Plan completed (phases P1-P5). 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 4 domain reports, which contain the answers to the research questions of the assessment elements of each domain. The structure of the domain reports includes: a chapter for research questions, the results (containing information on all assessment elements selected), and a domain discussion. The discussion section should cover the interpretation of the findings, issues that may affect the findings (the quality of the evidence, related uncertainties and the applicability of the evidence), evidence gaps and related questions.

Further relevant questions on patient and social aspects may be added (following the Checklist for potential ethical, organisational, patient and social and legal aspects included in the Project Plan).

Authors and co-authors could use the Online Tool Services (HTA Core Model® Online; https://meka.thl.fi/htacore/Logon.aspx) for the development of joint assessments. Instructions on how to use the Online Tool are provided in the user manual which can be found following this link: https://intranet.eunethta.eu/system/files/7_hta_core_model_online_tool_and_service.pdf.

In case the authors decide to work without using the Online Tool, the template to be used during the assessment phase is the “Rapid assessment template on other health technologies using the HTA Core Model for Rapid Relative Effectiveness Assessment”.

For guidance on how to collect and analyse data see section 2.3 of the Model for Rapid REA and the HTA Core Model.

3.9 A2 - Summary Section

The intention of the summary section is to present a meaningful overview of the domain reports. Special emphasis is on the aggregation of data on intended (effectiveness domain) and unintended (safety domain) effects in order to assess the net benefit. The benefits and harms of the intervention(s) should be presented in comparison with the comparator(s). Relevant results are summarised in a clear and easy-to-read format and visualised in the summary table of relative effectiveness. Authors formulate a conclusion including statements on effectiveness and safety of the technology in relation to the comparator(s). No recommendations regarding the reimbursement of the technology are included.

The following should be included in the summary:

- Scope
- Introduction: description of the technology; description of comparators; description of the health problem; description of the current treatment
- Methods: explanation of the mode of collaboration, general information on searches and sources used, tools and methods chosen for quality assessments and analyses, study types included for safety and clinical effectiveness domain, in case you have included assessment elements from other applications (i.e. for diagnostics or screening technologies) indicate which assessment elements you have included from which application
- 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.

3.10 A3 - Compiling the rapid assessment

First authors and co-authors compile a first version of the rapid assessment. One task is to screen for potential overlaps. The general structure of the assessment, according to the template is:

SUMMARY OF RELATIVE EFFECTIVENESS OF [XXX]
LIST OF ABBREVIATIONS
1 SCOPE
2 METHODS AND EVIDENCE INCLUDED
3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY
4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY
5 CLINICAL EFFECTIVENESS
6 SAFETY
7 ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS (OPTIONAL)
8 REFERENCES

APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED
APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS
APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

3.11 R - Internal Review phase

Authors send their first version of the rapid assessment to dedicated reviewers consisting of 2-5 WP5 Strand B members around the 35th day of the assessment phase.
Reviewers are prepared to dedicate their time and efforts towards a thorough reviewing process according to the timelines indicated in the Project Plan. They control the phases of the rapid assessment production, including a check of references and primary studies, a re-assessment of the risk of bias and the adherence to EUnetHTA Guidelines and processes. They send their comments to authors and co-authors within 10

working days using the standardised comments template for reviewers. The main task of dedicated reviewers is to ensure the high quality of the assessment.

(Co-)Authors are prepared to process the reviewers' comments and possible suggestions for changes within the next 15 working days. After finalising the 2nd draft of the assessment, authors send their feedback to dedicated reviewers. The comments from dedicated reviewers will be published, together with the authors' answers, on the EUnetHTA homepage together with the final assessment.

Of note, the indicated timeframes are a proposal but are not mandatory - deviations may occur.

3.12 C - External Review and consultation

The external review as well as the consultation phase should start around the 60th day of the rapid assessment production process. The CT sends the second and confidential draft of the rapid assessment to at least 2 clinical experts, Strand B members, the manufacturer(s) and possibly also to other stakeholders (e.g. European Federations of Physicians or/and Patients).
All consulted parties know the timelines beforehand, as communicated in the Project Plan, and are ready to provide their input within 15 working days using the consultation templates. All comments received are answered by the authors and co-authors in a standardised way to be published together with the final version of the assessment.

After the external review, authors produce the third version of the rapid assessment within 15 working days. The third version of the rapid assessment is sent to Medical Editing for a period of 10 working days.
The authors then work on the final version on the assessment. This version is sent to the CT for further technical and editorial amendments and for formatting after an additional 10 working days.

The rapid assessment should be ready for publication around the 120th day of the process. At the same time, dedicated reviewers and other WP5 members put their efforts into national adaptation of the rapid assessment into national/local reports. Of note, the indicated timeframes are a proposal but are not mandatory - deviations may occur.

3.13 E - Evaluation phase

This phase includes the evaluation of lessons learned during the rapid assessment by collecting information and opinions through a range of standardised surveys. The objective of this phase is to gather recommendations for continuously improving processes.

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

- assessment teams' perception about the cross-border collaboration in producing a rapid assessment by using a standardised survey
- WP5 Strand B members' perception on the usability/readability of the rapid assessments by using a standardised survey
- the duration of the assessment, the workload (in terms of working hours).

4 Appendix 1: Definitions

Back to Introduction

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

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

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

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

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

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

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: Core HTA information refers to any information on health technologies that has been produced using the HTA Core Model® in one of its applications.

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: A model that was developed to conduct rapid relative effectiveness assessments. A rapid assessment is an assessment of a technology within a limited timeframe in comparison with one or more relevant alternative interventions. It can be the assessment of a new technology launched into the market, or the (re)assessment of a technology for a new indication or when new relevant data are available. The model for rapid REA contains 4 of the 9 domains of the HTA Core Model® (first 4 domains). For these domains a subset of the assessment elements of the HTA Core Model® are included.

5 Appendix 2: Templates

Back to Introduction

5.1 Call for Collaboration Form

[Agencies name] is seeking agencies interested in collaborating on [proposed short title].

Authors:

Agency's name:	[State your agency's name]
Author's Name and contact details:	[Give the name(s) & contact details of the author(s)]

Project:

Proposed project title:	[Indicate the full title of the planned project]
Duration:	[Proposed start date (DD/MM/YYYY) – proposed end date (DD/MM/YYYY)]
Rationale:	[Please provide information why the topic has been selected for assessment, e.g. reimbursement decision)
Calling for:	[Authors for specific domains [indicate which domain/s], Co-author and Reviewers (choose the according roles you are looking for)]
Date of call:	[DD/MM/YYYY]
Expressions of interest:	
Until:	[Indicate the exact date (DD/MM/YYYY) until when you need expressions of interest – schedule 10 working days]
To whom:	If your agency is interested, answer to [add here the e-mail address of the main contact of your agency] and to [add here the e-mail address of the responsible person of the Coordinating team] and indicate which role (co-author, reviewer) your agency is interested in.

Proposed PICO Question:

Description	Project scope
Population	*Describe at least the population and the intervention, details on comparators and outcomes can be added already at this stage.*
Intervention	
Comparison	
Outcomes	

Proposed timetable for the rapid assessment:

Milestones/Deliverables	Start date	End date
Project duration	**[DD/MM/YYYY]**	**[DD/MM/YYYY]**
Scoping phase	[DD/MM/YYYY]	[DD/MM/YYYY]
Identification of manufacturer(s)	[DD/MM/YYYY]	[DD/MM/YYYY]
Scoping and development of draft Project Plan	[DD/MM/YYYY]	[DD/MM/YYYY]

Internal scoping e-meeting	[DD/MM/YYYY]	[DD/MM/YYYY]
Scoping (e-) meeting with manufacturer(s)	[DD/MM/YYYY]	[DD/MM/YYYY]
Consultation of draft Project Plan with dedicated reviewers	[DD/MM/YYYY]	[DD/MM/YYYY + 5 working days]
Amendment of draft Project Plan	[DD/MM/YYYY]	[DD/MM/YYYY + 5 working days]
Public consultation of draft Project Plan	[DD/MM/YYYY]	[DD/MM/YYYY + 15 working days]
Publication of final Project Plan and comments including assessment team's answers	[DD/MM/YYYY]	[DD/MM/YYYY + 10 working days]
Send request for draft Submission file template to manufacturer(s)	[DD/MM/YYYY]	[DD/MM/YYYY]
Completion of Submission file template by manufacturer(s)	[DD/MM/YYYY]	[DD/MM/YYYY + 30 working days]
Clarifying further questions concerning draft Submission file	[DD/MM/YYYY]	[DD/MM/YYYY + 10 working days]
Final Submission file	[DD/MM/YYYY]	[DD/MM/YYYY + 10 working days]
Assessment phase	[DD/MM/YYYY]	[DD/MM/YYYY]
Writing first draft rapid assessment	[DD/MM/YYYY]	[DD/MM/YYYY schedule approx. 35 working days]
Review by pool of ± 5 dedicated reviewers	[DD/MM/YYYY]	[DD/MM/YYYY + 10 working days]
Writing second draft rapid assessment	[DD/MM/YYYY]	[DD/MM/YYYY + 15 working days]
Review by ≥ 2 external clinical experts, WP5 Strand B members, manufacturer(s) and by other potential stakeholders	[DD/MM/YYYY]	[DD/MM/YYYY + 15 working days]
Writing third draft rapid assessment	[DD/MM/YYYY]	[DD/MM/YYYY + 15 working days]
Medical editing	[DD/MM/YYYY + 4 working days]	[DD/MM/YYYY + approximately 10 working days]
Writing of final version of rapid assessment	[DD/MM/YYYY]	[DD/MM/YYYY + 10 working days]
Formatting	[DD/MM/YYYY]	[DD/MM/YYYY + 5 working days]
Final version of REA		**[week** from DD/MM/YYYY - to DD/MM/YYYY]

5.2 Assessment element tables

ID	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	M P S D	–

ID	Topic	Issue	Clarification	Importance **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening	
				Mandatory	Non-mandatory
			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. Specific to screening technologies: 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?	–	M P S D

ID	Topic	Issue	Clarification	Importance **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening	
				Mandatory	Non-mandatory
			• 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? • 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 comparator(s) 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	M S D	P

ID	Topic	Issue	Clarification	Importance **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening	
				Mandatory	Non-mandatory
			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.		
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use 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 equipment and supplies are needed to use 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

ID	Topic	Issue	Clarification	Importance **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening	
				Mandatory	Non-mandatory
					D
2. Health problem and current use of technology					
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	M P S D	-

ID	Topic	Issue	Clarification	Importance **Abbreviations:** D=diagnostics; M=medical and surgical interventions; P=pharmaceuticals; S=screening	
				Mandatory	Non-mandatory
			care.		
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
A0025	Current	How is the disease or	It is important to describe whether the technology is an add-on or a replacement for the	M	–

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	management of the condition	health condition currently managed according to published guidelines and in practice?	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.	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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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	–

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			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. <u>Specific to diagnostic technologies:</u> In diagnostic and screening technologies, this issue refers to the expected beneficial effect of the test-treatment chain. <u>Specific to screening technologies:</u> 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.		

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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 – 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	–

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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	–

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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 – 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	M P	–

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			of follow-up. 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?	S 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 – Safety.	P	M S D

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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
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 – Safety.	–	M P S D

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B0010	Safety risk management	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator(s)?	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-sharing scheme that innovative pharmaceuticals require in some countries. Notice also the requirements of pharmacovigilance monitoring.	M	P S D

Further Assessment elements for diagnostic and screening technologies only

ID	Topic	Issue	Clarification	Importance	
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)

ID	Topic	Issue	Clarification	Importance	
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 results and the subsequent false-negative diagnostic test results.	D S	-