



eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA WP5 Joint Action 2

Apply(ing) the HTA Core Model for Rapid Assessment for national/local adaptation and reporting

PROCEDURE MANUAL WP5 STRAND A: RAPID RELATIVE EFFECTIVENESS ASSESSMENT OF PHARMACEUTICALS

V4, April 2015

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.

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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

Introduction

Objective of this manual:

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

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 (transportation) 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 7 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.

- 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:

- the 'Model for Rapid Relative Effectiveness Assessment (REA) of pharmaceuticals

The relevant model to be used for production of rapid REAs within WP5 EUnetHTA JA2 is the model for rapid REA of pharmaceuticals

[http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf]. On the basis of the experience gained during the production of the pilots, the model for rapid REA of pharmaceuticals will be updated as an additional result of WP5 JA2. This update is planned for the end of 2014.

- 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.

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.

Process of the pilots

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

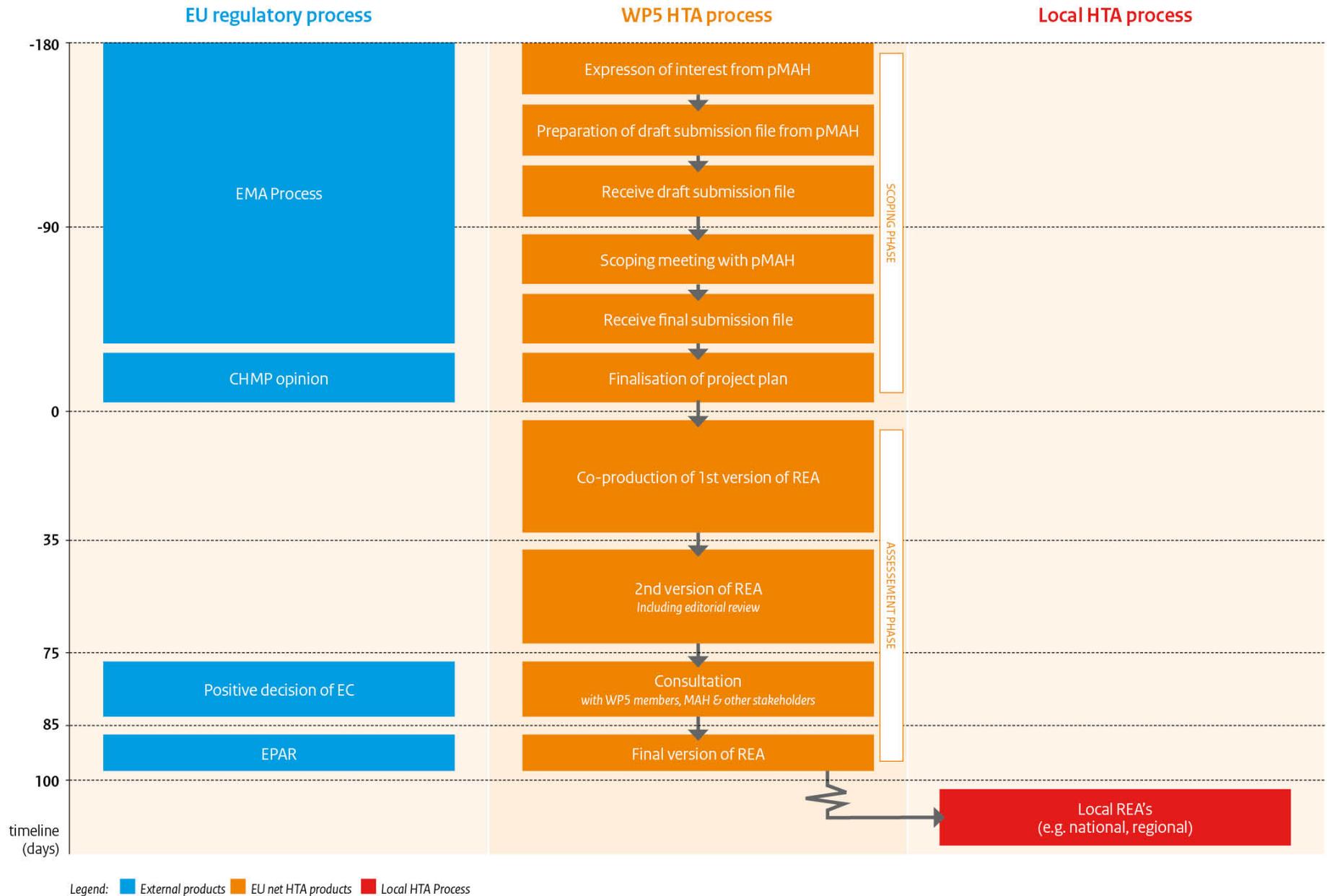


Figure 2: Schematic overview of the Scoping Phase

It should be noted that these graphs represent the ideal picture; however, divergence is very possible for specific joint REA's

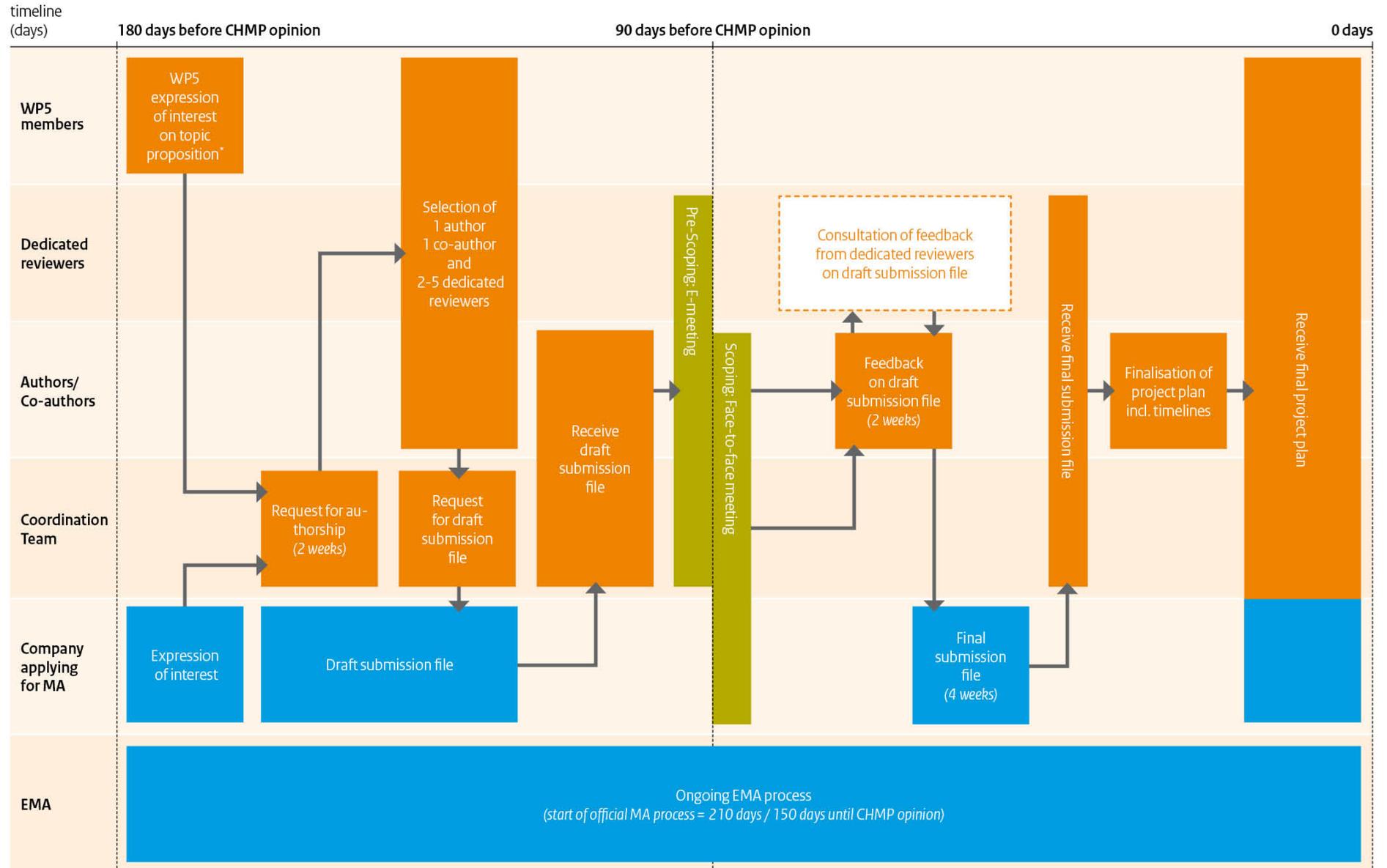


Figure 3: Schematic overview of the Assessment Phase

It should be noted that these graphs represent the ideal picture; however, divergence is very possible for specific joint REA's

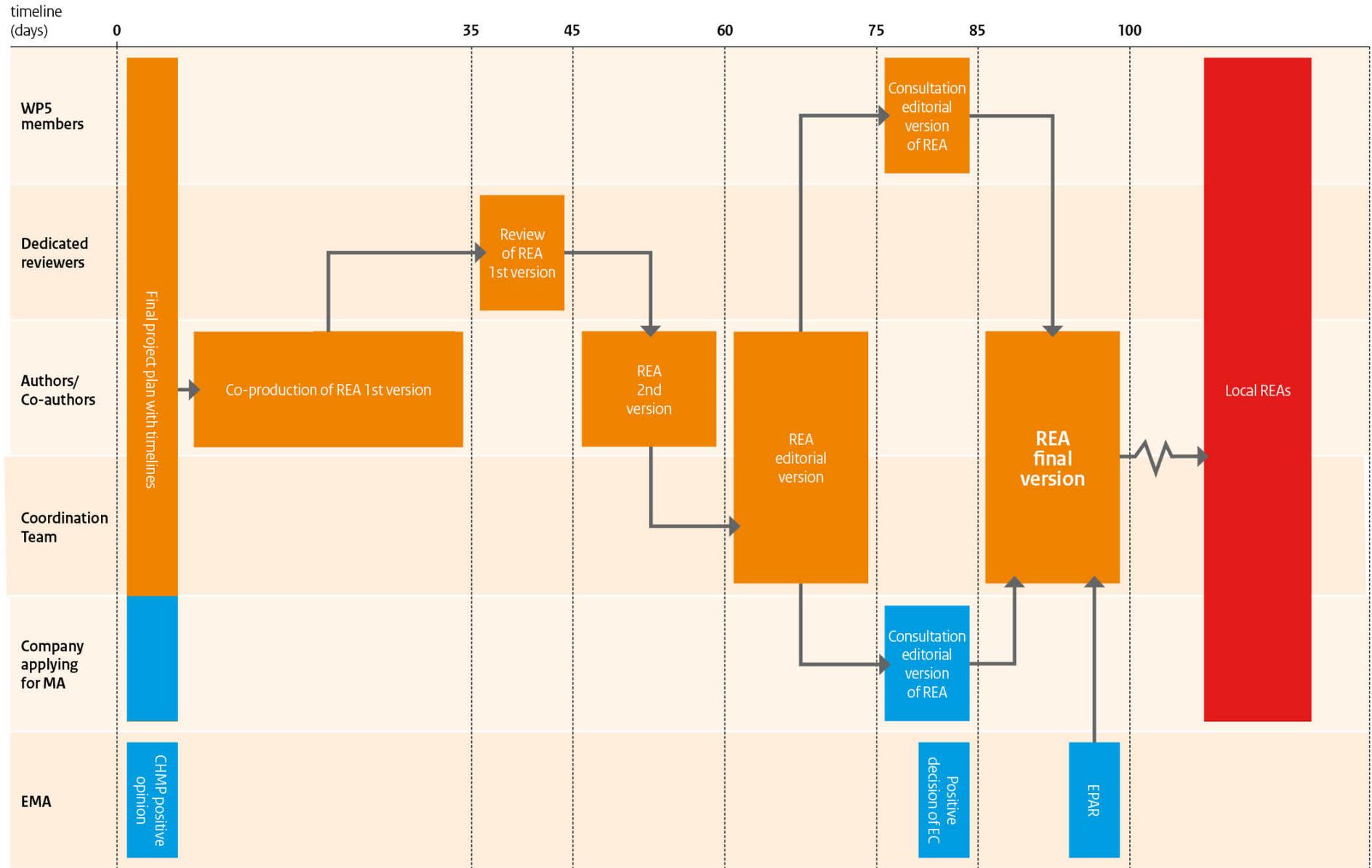


Table 1. Schedule of the pilots

Scoping				
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 1 st 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

REA 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
45	75	Writing second draft report, including editorial review	WP5 Strand A members, Manufacturer, other stakeholders	Author/Co-author, Editor

REA phase				
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

Pilots' 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 (ZIN)

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 by 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.

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.

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.eunetha.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.

P0 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.

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 manufacturer's REA submission file should be used as the basic source for scoping. 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.

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: \[http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf\]\(http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf\)](http://www.eunetha.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-dependent context

For a detailed explanation of how to proceed see section 2.4 of the [HTA Core Model for Rapid REA: \[http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf\]\(http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf\)](http://www.eunetha.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.eunetha.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)**,

A5 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.

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
ID	The 5 digit identification code of the assessment element
Research question	Copy the research question from Table 5 in the project plan
Methods	<p>In this section you should report the methods that you actually used for answering the research questions.</p> <ul style="list-style-type: none"> • 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

	<p>use GRADE or other instrument to provide overall view of the results.</p> <p>Mark citations in the text in the form of: [Surname of first author Year].</p> <p>Please note that this part should only focus on results, i.e. presentation of data, not interpretation.</p>
Discussion	Use this field to add comments for the methods used, or the reliability of the results. E.g. problems identified in identifying or quality of information, pending research, or need for further research.
References	<p>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 .</p> <p>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.</p>

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.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf):
http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf

A6 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.

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

A7 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

R8 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).

C9 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

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

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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).